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Provisional Peer-Reviewed Toxicity Values for

Sulfolane
(CASRN 126-33-0)

Superfund Health Risk Technical Support Center
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Office of Research and Development
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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMD	benchmark dose
BMCL	benchmark concentration lower bound 95% confidence interval
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
POD	point of departure
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete-to-complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR SULFOLANE (CASRN 126-33-0)

BACKGROUND

HISTORY

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) EPA's Integrated Risk Information System (IRIS)
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in EPA's Superfund Program
3) Other (peer-reviewed) toxicity values, including
   - < Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR);
   - < California Environmental Protection Agency (CalEPA) values; and
   - < EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by a panel of six EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

DISCLAIMERS

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

Sulfolane (2,3,5-tetrahydrothiophene-1,1-dioxide; tetramethylene sulfone), CAS No. 126-33-0, is used as an industrial solvent as well as in polymer manufacturing and electronics. It is listed as a high production volume chemical by the Organisation for Economic Cooperation and Development (OECD, 2004). Sulfolane has a low vapor pressure, suggesting it has low volatility; however, it is highly soluble in water. A table of physicochemical properties is provided below (see Table 1).

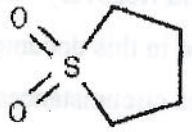

Figure 1. Sulfolane Structure

Table 1. Physicochemical Properties Table for Sulfolane[a] (CASRN 126-33-0)

Property (unit)	Value
Boiling point (°C)	285
Melting point (°C)	27.4–27.8
Density (g/cm^3)	1.265
Vapor pressure (mm Hg at 27.6°C)	0.0062
pH (unitless)	ND
Solubility in water (g/L at 25°C)	≥100[b]
Relative vapor density (air = 1)	1.266[b]
Molecular weight (g/mol)	120.18

[a]ATSDR (2010a).
[b]OECD (2004).
ND = no data.

No Reference Dose (RfD), Reference Concentration (RfC), or cancer assessment for sulfolane is included on the United States Environmental Protection Agency (U.S. EPA) Integrated Risk Information System (IRIS) (U.S. EPA, 2010) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2009). No RfD or RfC values were reported in

the Health Effects Assessment Summary Tables (HEAST, 2003). The Chemical Assessments and Related Activities (CARA) list did not include a Health and Environmental Effects Profile (HEEP) for sulfolane; there are no noncancer toxicity values (U.S. EPA, 1994). The toxicity of sulfolane has not been reviewed by the Agency for Toxic Substances and Disease Registry (ATSDR) in a Toxicological Profile (ATSDR, 2010b), but ATSDR did perform a Health Consultation on sulfolane for the Alaska Department of Health and Social Services. ATSDR recommended an oral exposure limit of 2.5 µg/kg-day based on an oral subchronic study in guinea pigs by Zhu et al. (1987) (ATSDR, 2010a). The toxicity of sulfolane has not been reviewed by the World Health Organization (WHO, 2010). The California Environmental Protection Agency (CalEPA, 2008, 2009a) has not derived toxicity values for exposure to sulfolane. No occupational exposure limits for sulfolane have been derived by the American Conference of Governmental Industrial Hygienists (ACGIH, 2010), the National Institute of Occupational Safety and Health (NIOSH, 2005), or the Occupational Safety and Health Administration (OSHA, 2010).

The HEAST (U.S. EPA, 2003) does not report any values for cancer or a cancer weight-of-evidence classification for sulfolane. Sulfolane has not been evaluated under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005). The International Agency for Research on Cancer (IARC, 2010) has not reviewed the carcinogenic potential of sulfolane. Sulfolane is not included in the *11th Report on Carcinogens* (NTP, 2005). CalEPA (2009b) has not prepared a quantitative estimate of carcinogenic potential for sulfolane.

Literature searches were conducted on sources published from 1900 through October 12, 2010 for studies relevant to the derivation of provisional toxicity values for sulfolane, CAS Number 126-33-0. Searches were conducted using EPA's Health and Environmental Research Online (HERO) evergreen database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications (NSCEP) and National

Environmental Publications Internet Site (NEPIS) database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI, and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); World Health Organization; and Worldwide Science. The following databases outside of HERO were searched for risk assessment values: ACGIH, ATSDR, CalEPA, EPA IRIS, EPA HEAST, EPA HEEP, EPA OW, EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides an overview of the relevant database for sulfolane and includes all potentially relevant repeated short-term, subchronic, and chronic duration studies. NOAELs, LOAELs, and BMDL/BMCL are provided in HED/HEC units for comparison except that oral noncancer values are not converted to HEDs and are identified in parentheses as (Adjusted) rather than HED/HECs. Principal studies are identified. Following the table, important aspects of all the studies in the table are provided in the same order as the table. Reference can be made to details provided in Table 2. The phrase "statistical significance", used throughout the document, indicates a p-value of <0.05, unless otherwise noted.

Table 2. Summary of Potentially Relevant Data for Sulfolane (CASRN 126-33-0)

Notes[a]	Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[b]	Critical effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (Comments)
Human								
				1. Oral (mg/kg-d)[b]				
NA	Subchronic	ND						
NA	Chronic	ND						
NA	Developmental	ND						
NA	Reproductive	ND						
NA	Carcinogenicity	ND						
				2. Inhalation (mg/m^3)[b]				
NA	Subchronic	ND						
NA	Chronic	ND						
NA	Developmental	ND						
NA	Reproductive	ND						
NA	Carcinogenicity	ND						
Animal								
				1. Oral (mg/kg-d)[b]				
PS NPR	**Subchronic**	**10/10, CD, Rat, drinking water, 13 wk**	**2.1, 8.8, 35.0, 131.7 (males)** **2.9, 10.6, 42.0, 191.1 (females)**	**Significant reductions in total white blood cell (WBC) and differential WBC counts (lymphocyte, basophils, monocyte, and large unstained cell [LUC]) counts in females; increased incidence and severity of cortical tubules with hyaline droplets in the kidneys of males**	**8.8 (males)** **2.9 (females)**	**No models fit to data (reduced white blood cells in females)**	**35.0 (males)** **10.6 (females)**	**Huntingdon Life Sciences (2001)**

Table 2. Summary of Potentially Relevant Data for Sulfolane (CASRN 126-33-0)

Notes[a]	Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[b]	Critical effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (Comments)
PR	Subchronic	6–12/6–12, Crj:CD(S-D), Rat, gavage, 28 d	0, 60, 200, or 700	Slight reduction of locomotor activity and splenic weight in females; increased relative kidney weight in males; decreased body weight and food consumption in males and females; increased hyaline droplets and eosinophilic bodies in renal tubules of males	60 (male hyaline droplets in kidney) 200 (female decreased spleen weight)	267 (female spleen weight)	200 (male hyaline droplets in kidney) 700 (female decreased spleen weight)	Ministry of Health and Welfare Japan (1996a) as cited by OECD (2004)
PR	Subchronic	80 unspecified sex, and strain, Rat, unspecified oral exposure, 90 d	0, 55.6, 167, or 500	Decreased urine volume, increased urine gamma glutamyl transferase activity, decreased serum alkaline phosphatase, decreased "ICD," decreased thrombin.	NDr[c]	NDr	NDr[c]	Zhu et al. (1987a)
PR	Subchronic	80 unspecified sex and strain, Guinea Pig, unspecified oral exposure, 90 d	0, 55.6, 167, or 500	Decreased ascorbic acid content in adrenal glands; decreased serum alkaline phosphatase levels; decreased white blood cell count	NDr[c]	NDr	NDr[c]	Zhu et al. (1987b)
PR	Subchronic	20/20, unspecified strain, Guinea Pig, unspecified oral exposure, 3 mo interim sacrifice	0, 0.25, 2.5, 25, or 250	Decreased marrow cell counts; shrinkage of the white pulp in the spleen	NDr[c]	NDr	NDr[c]	Zhu et al. (1987c)
PR	Chronic	20/20, unspecified strain, Guinea Pig, unspecified oral exposure, 6 mo	0, 0.25, 2.5, 25, or 250	Shrinkage of the white pulp in the spleen; fatty degeneration of liver	0.25	NDr	2.5	Zhu et al. (1987c)

Table 2. Summary of Potentially Relevant Data for Sulfolane (CASRN 126-33-0)

Notes[a]	Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[b]	Critical effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (Comments)
PR	Developmental	Unreported number of females, Kuenming, Mouse, unreported method of oral administration, GD 6–15	0, 93, 280, 840	Increased fetal resorption; skeletal abnormalities (breastbone malposition, rib fusion)	280 (maternal and developmental)	NDr	840 (maternal and developmental)	Zhu et al. (1987d)
PR	Reproductive	12/12, Crj:CD(S-D), Rat, gavage, 49 d (males), 41–50 d (females)	0, 60, 200, 700	Mortality; decreased number of estrous cases; entire litter loss during lactation; increased number of still births; decreased body weight gain and food consumption in males and females (premating); decreased birth index and number of viable pups on Days 0 and 4 of lactation	60 (reproductive and developmental)	NDr	200 (reproductive and developmental)	Ministry of Health and Welfare Japan (1999) as cited by OECD (2004)
NA	Carcinogenicity	ND						
				2. Inhalation (mg/m^3)[b]				
PR	Subchronic	8/7, S-D, Rat, repeated exposure, 8 hr/d, 5 d/wk, 37 d	120	Chronic liver inflammation; chronic lung inflammation	NA	NDr	120	Andersen et al. (1977a)
PR	Subchronic	15/0, 15/0, 8/7, S-D, Rat, continuous exposure, 23 hr/d, 90–110 d	2.7, 3.8, 19.2	No effects observed	19.2	NDr	NA	Andersen et al. (1977b)
PR	Subchronic	8/7, Hartley, Guinea Pig; repeated exposure, 8 hr/d, 5 d/wk, 37 d	120	Chronic lung inflammation	NA	NDr	120	Andersen et al. (1977c)

Table 2. Summary of Potentially Relevant Data for Sulfolane (CASRN 126-33-0)

Notes[a]	Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[b]	Critical effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (Comments)
PR	Subchronic	15/0, 15/0, 8/7, 24/24, 15/15, Hartley, Guinea Pig, continuous exposure, 23 hr/d, 85–110 d	2.7, 3.8, 19.2, 152, and 192	Chronic pleuritis; white blood cell count significantly lower than preexposure levels; fatty vacuolation of the liver	152	NDr	192	Andersen et al. (1977d)
PR	Subchronic	2/0, Beagle, Dog, repeated exposure, 8 hr/d, 5 d/wk, 37 d	120	Chronic lung inflammation	NA	NDr	120	Andersen et al. (1977e)
PS PR	**Subchronic**	**1–4 males/group, Beagle, Dog, continuous exposure, 23 hr/d, 85–110 d**	**2.7, 3.8, 19.2, and 192**	**Convulsions, labored breathing, and aggressive behavior in all dogs; severe motor seizures; severe convulsion; chronically inflamed and hemorrhagic lungs**	**19.2**	**NDr**	**192 (FEL)**	**Andersen et al. (1977f)**
PR	Subchronic	9/0, Squirrel Monkey (*Saimiri sciureus*), repeated exposure, 8 hr/d, 5 d/wk, 37 d	120	Chronic lung inflammation; extreme convulsions; blood-tinged fluid around eyes; pale livers and hearts; fatty metamorphosis of the liver	NA	NDr	120 (FEL)	Andersen et al. (1977g)
PR	Subchronic	2–9 males/group, Squirrel Monkey, continuous exposure, 23 h/d, 85–110 d	2.7, 3.8, 19.2, and 192	Mortality and moribundity; chronic pleuritis	19.2	NDr	192 (FEL)	Andersen et al. (1977h)
NA	Chronic	ND						
NA	Developmental	ND						

Table 2. Summary of Potentially Relevant Data for Sulfolane (CASRN 126-33-0)

Notes[a]	Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[b]	Critical effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (Comments)
NA	Reproductive	ND						
NA	Carcinogenicity	ND						

[a]Notes: IRIS = Utilized by IRIS, date of last update; PS = Principal study, PR = Peer Reviewed, NPR = Not peer reviewed.
[b]Dosimetry: NOAEL, BMDL/BMCL and LOAEL values of long-term exposure (4 weeks and longer) are converted from a discontinuous to a continuous (weekly) exposure. Values from animal developmental studies are not adjusted to a continuous exposure. Values for inhalation were not converted to HEC for respiratory effects due to inadequate information available on particle size of the vapor or for any similar vapor.
[c]Incomplete results and lack of description precludes assigning effect levels to the subchronic portion of this study.
NA = not applicable, NDr = Not determined, FEL = Frank effect level.

HUMAN STUDIES

Oral Exposures

The effects of oral exposure of humans to sulfolane are not identified in the literature.

Inhalation Exposures

The effects of inhalation exposure of humans to sulfolane are not identified in the literature.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure of animals to sulfolane have been evaluated in several subchronic (Huntingdon Life Sciences, 2001; Ministry of Health and Welfare Japan, 1996 as summarized in ATSDR, 2010a; Zhu et al., 1987), one 6-month chronic (Zhu et al., 1987), one developmental (Zhu et al., 1987), and one screening-level reproductive study (Ministry of Health and Welfare Japan, 1999, as summarized in ATSDR, 2010a). No carcinogenicity studies of animals orally exposed to sulfolane are identified in the literature.

Subchronic Studies

Huntingdon Life Sciences (2001)

The 13-week drinking water study in rats (Huntingdon Life Sciences, 2001) is selected as the principal study for derivation of the screening subchronic and screening chronic p-RfD. In a GLP-compliant, non peer-reviewed study by Huntingdon Life Sciences (2001), study authors administered sulfolane (purity unreported) to CD rats (10/sex/group) in drinking water at concentrations of 0, 25, 100, 400, or 1600 mg/L for 13 weeks. Authors calculated the achieved dosages as 2.1, 8.8, 35.0, and 131.7 mg/kg-day, respectively, for males and 2.9, 10.6, 42.0, and 191.1 mg/kg-day, respectively, for females. Analytical measurements performed by study authors indicated that sulfolane was stable in drinking water for 8 days at ambient temperatures and that achieved formulations were within acceptable limits (96.3–109% of nominal concentrations). Animals were 26–30 days old when supplied by Charles River (UK) Limited, Margate, Kent, England. At the beginning of treatment, animals were 39–43 days old. Males weighed 167–215 grams, and females weighed 142–180 grams.

Animals were housed in a highly controlled environment. Temperatures were kept between 19–23°C and relative humidity was kept between 40–70%. Lighting was supplied in a 12 hour light/dark cycle. The rodent facility was designed and maintained to prevent contamination with external biological and chemical agents. Rats were kept in stainless steel cages with five rats of the same sex in each cage. Food (Rat and Mouse No. 1 Maintenance Diet, Special Services, Ltd., Witham, Essex, England) was provided freely, except on nights before blood sampling. Public tap water was supplied ad libitum in polycarbonate water bottles. Diet and water analyses did not indicate any signs of contamination that may have affected the study.

Study authors examined animals at least twice per day for treatment-related effects and disease. Detailed physical examinations were performed once per week for each animal. Body weight was recorded during acclimatization, at Week 0, once per week throughout treatment, and again at study termination. Food consumption was measured by weighing supplied food and measuring spilled food. Mean weekly consumption and food conversion efficiency were calculated using these data. Water consumption was recorded weekly. All animals were given eye examinations before treatment, focusing on the adnexa, conjunctivae, cornea and sclera, anterior chamber and iris, lens and vitreous, and ocular fundus. Any animals with ocular abnormalities were replaced with healthy animals. During Week 13 of treatment, study authors examined the eyes of animals in the control and high-dose groups.

Study authors performed functional observational battery tests at various times throughout the study. Before treatment and once weekly throughout treatment, animals were examined in the hand for exophthalmos, fur condition, lacrimation, piloerection, reactivity to handling, ease of removal from cage, salivation, and vocalization on handling. Afterward, activity counts, arousal, convulsion, defecation count, gait, grooming, palpebral closure, posture, rearing count, tremor, twitches, and urination were assessed during a one-minute period in a standard area. Before treatment and during Weeks 6 and 12, animals were examined for approach response, auditory startle reflex, body temperature, body weight, grip strength (forelimbs and hindlimbs), landing foot splay, tail pinch response, pupil reflex, righting reflex, and touch response. Motor activity was measured before treatment and during Weeks 6 and 12 using infrared sensor equipment on animals for 1 hour.

During Week 13, blood samples were collected and examined for hematocrit, hemoglobin, erythrocyte count, total and differential leukocyte count, platelet count, mean cell hemoglobin (MCH), mean cell volume (MCV), and mean cell hemoglobin concentration (MCHC). Romanowsky stains of blood films were examined using light microscopy for abnormal morphology and unusual cell types. Prothrombin time (PT) and activated partial thromboplastin time (APTT) were also measured in additional samples. Blood cell counts also reported large unstained cells (LUC) which are thought to be larger than normal or atypical lymphocytes. During Week 13, blood plasma was analyzed for alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, total cholesterol, creatinine, urea, total protein, albumin, albumin/globulin ratio, and sodium and potassium concentrations.

At sacrifice, study authors performed a full necropsy including examination of the external body and orifices; neck; and cranial, thoracic, abdominal, and pelvic cavities including their viscera. Study authors recorded organ weights (with bilateral organs weighed together) for the adrenals, brain, epididymides, heart, kidneys, liver, ovaries, spleen, testes, thymus, and uterus with cervix. The following organs were preserved with 10% neutral buffered formalin (except testes and epididymides, which were preserved in Bouins fluid and then 70% industrial methylated spirits) and examined microscopically: adrenals, aorta, brain, cecum, colon, duodenum, epididymides, femur (with joint), heart, ileum, jejunum, kidneys, liver, lungs (with bronchi), lymph nodes, mammary area, esophagus, ovaries, pancreas, pituitary, prostate, rectum, salivary gland, sciatic nerve, seminal vesicles, skin, spinal cord, spleen, sternum, stomach, testes, thymus, thyroid with parathyroids, trachea, urinary bladder, and uterus with cervix.

In control and high-dose animals, tissue samples were sectioned and stained from the adrenals (cortex and medulla), brain (cerebellum, cerebrum, and midbrain), femur, heart, ileum, kidneys, liver, lungs, mammary area (including overlying skin), spinal cord, stomach, thyroid, uterus, and testes. The study report indicates that kidneys were examined in the 2.1, 8.8, 35.0 mg/kg-day groups (males) and 2.9, 10.6, 42.0 mg/kg-day groups (females). Study authors also examined any abnormal tissues observed in control and all treatment groups.

Study authors did not observe any deaths or treatment-related clinical signs in either males or females. Study authors did not observe treatment-related findings in bodyweight (see

Table B.1), food and water consumption, ocular examinations, functional observational battery tests, organ weight, or macroscopic tissue examination in males or females. Food conversion efficiency was slightly lower than controls during Week 1 in animals receiving the highest dose level (see Table B.2). However, after this time point, food efficiency was comparable to controls in all groups. Females receiving 2.9 mg/kg-day of sulfolane had increased body weight gain compared to controls, but the weight gain was not significant. Females exhibited statistically significant decreases in total white blood cells (WBC), lymphocyte, monocyte, basophil and large unstained cell (LUC) counts compared to controls in the 10.6, 42.0, and 191.1 mg/kg-day dose groups (see Table B.3). Information was not provided about neutrophils or other cell types, and it is assumed these did not change. Males did not experience similar decreases in these cell counts. There were other intergroup hematological differences reaching statistical significance, with little or no biological relevance, including slightly prolonged prothrombin times in high-dose males and increased mean cell volumes and reduced activated partial thromboplastin times in high-dose females. Large unstained cells (LUC) were significantly lower in males at 35.0 and 131.7 mg/kg-day compared to control, but study authors noted there were high values in two of the control animals.

Males in the high-dose group (131.7 mg/kg-day) experienced lowered ALT activities and elevated creatinine concentrations in Week 13 that were statistically significantly different than controls (see Table B.4). Males in the high-dose group had statistically significantly lower AST activities, but authors noted that the mean value in controls was higher due to unusually high levels in two animals. These differences were not deemed biologically significant by EPA. The high-dose males also displayed reduced plasma sodium concentration compared to controls, but study authors attributed this decrease to a very low value in one control animal.
Histopathological examinations indicated that males dosed with 35.0 and 131.7 mg/kg-day had an increasing incidence and severity of hyaline droplets in the cortical tubules of the kidneys; this effect was considered treatment related (see Table B.5). High-dose males also experienced a slightly elevated incidence of granular casts of the renal medulla compared to controls.

Sulfolane exposure of rats via the drinking water for 13 weeks was well tolerated, with kidneys and WBC as targets of toxicity. The kidney effects in males (hyaline droplets in cortical tubules and increased incidence of cortical tubule basophilia) fit basic criteria to be considered

related to male-specific alpha$_{2u}$globulin nephropathy, although study authors did not specifically stain kidney sections for evidence of alpha$_{2u}$globulin protein (as per U.S EPA, 1991). The effects seen in male and not female rats gives further indication that this type of nephropathy is likely present. The information absent from this analysis means that this effect cannot be automatically discounted as being not relevant to humans on the basis of being an alpha$_{2u}$ effect. Although there was no assay of functional manifestation of the white cell decreases such as decreased inflammation or compromised immune function, or other effects to the organs of the immune system, the decreases in white cell counts seen in female rats are broad (seen in several cell types), statistically significant, and dose-related. Additionally, there was a statistically significant decrease in the spleen weights at the high dose, which supports the immune suppression effect. Also, this effect has been consistently reported in several other studies of sulfolane exposures (albeit at higher exposures) in different strains of rat (Crj:CD[S-D]), species (guinea pigs) and routes of exposure (inhalation) (Zhu et al., 1987; Andersen et al., 1977). A BMD analysis of the male renal effects (hyaline droplet) is not attempted because the dose-response was nonmonotonic, and statistical analysis performed for this review indicates that incidence of hyaline droplet in cortical tubules at the highest dose was not statistically significantly different from control by Fisher's exact test (4/10 vs. 9/10, $p = 0.0573$). Finally, the endpoint based on leukocyte findings is more sensitive than the kidney effects.

Attempts to model the total and differential WBC data were not successful or gave results that were extremely insensitive with respect to the observable NOAEL (see Appendix A) such that a NOAEL of 2.9 mg/kg-day is designated from these data. As the biological relevance of male rat kidney findings is of somewhat questionable relevance to human health and since the changes in the leukocyte types is a consistently observed effect, a NOAEL of 2.9 mg/kg-day in females is established as a POD for deriving the screening oral subchronic and chronic RfD. The LOAEL in females is 10.6 mg/kg-day.

Ministry of Health and Welfare Japan (1996a, cited in OECD, 2004)

In a GLP-compliant, peer-reviewed study, the Ministry of Health and Welfare Japan (1996a, cited in OECD, 2004) administered sulfolane (vehicle and purity unreported) by gavage to 5-week old male and female Crj:CD(S-D) rats (source unreported) at dose levels of 0, 60, 200, or 700 mg/kg-day for 28 days. The study report was written in Japanese but is summarized here

based on secondary information from the Organisation for Economic Cooperation and Development (OECD, 2004). Additionally, the data tables in the Ministry of Health and Welfare Japan study report are available in English. There were 6 animals/sex in the 60 and 200 mg/kg-day groups and 12 animals/sex for the groups dosed at 0 and 700 mg/kg-day. After 28 days of treatment, 6 animals in the control and 6 in the 700 mg/kg-day groups were observed for a 14-day recovery period. The exact methods, animal husbandry, and statistical procedures performed by the Ministry of Health and Welfare Japan were not reported by the OECD.

There were no deaths in the control or treatment groups. Males in the 700 mg/kg-day group experienced significantly ($p < 0.01$) lower absolute body weight compared to controls throughout treatment (12–14% body weight depression from Days 3–28), while high-dose females only differed significantly ($p < 0.01$) from controls for the first 14 days of treatment (11% absolute body weight depression only on Day 3) (see Table B.6). Males experienced significantly ($p = 0.01$) decreased food consumption for the first 3 weeks of treatment, while females had significantly ($p < 0.01$) decreased food consumption the first week of treatment and in the first week of recovery (see Table B.7). High-dose females experienced decreased locomotor activity (3/12 animals; see Table B.8) during the beginning of the treatment period. Hematology revealed that all dosed male groups had significantly ($p < 0.05$) slightly decreased (2–3%) mean cell hemoglobin concentration (MCHC) after 28 days of treatment, but there was no decrease observed after the 14-day recovery period. White blood cell counts (WBC) in males of the high-dose group were significantly higher ($p < 0.05$) compared to control only after the recovery period and not after the 28-day treatment period. Since only the control and the high dose groups were examined after recovery, a dose-response could not be evaluated. Effects on WBC in treated females were not observed. High-dose females had significantly reduced mean red blood cell counts (RBC) and significantly increased mean cell volume (MCV) compared to controls after recovery (see Table B.9) but the biological relevance is questionable since these changes were less than 5%. The high dose males had decreased chloride (<2%) and increased cholinesterase activity (60%) and total bilirubin (29%) but all three parameters returned to normal after the recovery period. The high dose females had elevated ALT (146% of control) and decreased glucose (85% of control) (see Table B.10). Males experienced increased relative kidney weight (see Table B.11) and increased incidence and severity of hyaline droplets and eosinophilic bodies in the renal tubules at both 200 and 700 mg/kg-day (see Table B.12). While

high-dose females had lowered spleen and liver weights, these effects were not accompanied by histological abnormalities. The kidneys of treated animals recovered, and other treatment-related changes appeared to reverse after a 14-day recovery period. Based on observed effects including white blood cell decreases, OECD established a NOAEL of 60 mg/kg-day for males and 200 mg/kg-day for females.

Zhu et al. (1987)

In a single, published study that was translated from Chinese for this review, Zhu et al. (1987) conducted a series of studies on the acute, subchronic (90-day), and chronic (6-month) oral toxicity of sulfolane in mice, white rats, and guinea pigs. Study authors also conducted a teratogenicity test and several genotoxicity tests (Ames, bone marrow micronucleus test, and sister chromatid exchange test). The studies are referred to as Zhu et al. (1987a) for the subchronic test on white rats, Zhu et al. (1987b) for the subchronic test on guinea pigs, Zhu et al. (1987c) for the chronic, 6-month toxicity test on white rats, Zhu et al. (1987d) for the developmental toxicity test, and Zhu et al. (1987e) for the genotoxicity tests. The Zhu et al. (1987) study is considered a peer-reviewed study because it was reviewed in a Health Consultation by ATSDR (2010a). Study authors did not state whether the experiment adhered to GLP guidelines and did not provide data tables in the translation. This report appears to be an extended abstract of the original study with very little useful information for risk assessment purposes. There is, for example, no clear indication of histopathological examination of any tissues in any test described, save for the spleen and liver in the 6-month study. This lack of results precludes assigning any effect levels at least to the 90-day test reports.

Zhu et al. (1987a)

Zhu et al. (1987a) conducted an oral toxicity study on 80 white rats (sex, age, strain not specified) at doses of 0, 55.6, 167, or 500 mg/kg-day sulfolane (purity, vehicle not specified) for 90 days. Study authors did not specify the type (e.g., gavage, drinking water, diet) or frequency of oral administration. It is unclear from the translated study report whether the dosing units were reported as mg/kg food or mg/kg body weight; however, the review by ATSDR (2010a) cites the units as mg/kg body weight per day. After 90 days, study authors sacrificed animals by femoral artery bleed and measured biochemical parameters, "organ index," and pathology with no mention of histopathology. Study authors did not delineate the specific biochemical

parameters examined, nor did they specify the meaning of "organ index." Additionally, study authors did not provide data tables or report the type of statistical procedures performed, but they did provide *p*-values to indicate statistical significance.

In rats, no significant changes in biochemical or pathology were reported in the low and mid-dose groups. However, study authors reported significant changes in the high-dose group (500 mg/kg-day) including: increased urine volume, increased gamma glutamyl transferase activity in the urine, decreased serum alkaline phosphatase (ALP) activity, decreased ICD (undefined in the study report, but likely serum isocitrate dehydrogenase), and decreased thrombin. The study authors stated that other examined parameters did not change significantly.

Zhu et al. (1987b)

Zhu et al. (1987b) conducted an oral toxicity study on 80 guinea pigs total (sex, age, group size, strain not clearly indicated) at doses of 0, 55.6, 167, or 500 mg/kg-day sulfolane (purity, vehicle not specified) for 90 days (see description of doses in Zhu et al., 1987a). After 90 days, study authors sacrificed animals by femoral artery bleed and measured specific biochemical parameters, "organ index," and pathology with no mention of histopathology. Study authors did not delineate the specific biochemical parameters examined, nor did they specify the meaning of "organ index." Additionally, study authors did not report the type of statistical procedures performed, but they did provide *p*-values to indicate statistical significance. In guinea pigs, white blood cell counts were significantly ($p < 0.05$) decreased relative to controls values in all dose groups, although no other indication of dose-response is described or given.

Chronic Study

Zhu et al. (1987c)

Study authors conducted a 6-month, chronic toxicity study where guinea pigs (20/sex/dose) were orally dosed with sulfolane (vehicle and purity not reported) at dose levels of 0, 0.25, 2.5, 25, or 250 mg/kg-day. The translation of the study did not specify the type or frequency of oral exposure (e.g., gavage, diet, drinking water). Study authors conducted biochemical and pathological evaluations on a subset of animals during an interim sacrifice at 3 months and at the end of the study at 6 months. This information is the only experimental

design information provided in the translation. The translation did not state the specific biochemical parameters, organs examined, or whether the "pathology" mentioned was gross pathology or histopathological. The study authors did not provide data tables; however, study authors did provide some values for biochemical parameters and incidence of pathology in the written narrative. The translated study did not mention any methods for statistical analysis. The data from the interim sacrifice at 3 months is considered subchronic data.

At the 3-month interim sacrifice, study authors reported that ALT, AST, and marrow cell number were lower than controls (see Table B.12). It is not clear from the study report which values were statistically significant. Incidence for shrinkage of white pulp in the spleen in the 0, 0.25, 2.5, 25, and 250 mg/kg-day groups were reported as 0/14, 0/14, 1/14, 2/14, and 6/14, respectively. Study authors did not present any statistical analysis on data for incidence of white pulp shrinkage in the spleen. Shrinkage in this area may be related to decreased cellularity, which may occur after exposure to agents that cause necrosis of lymphocytes, T-lymphocytes in particular (Elmore, 2006). At 6 months, study authors reported that the "organ coefficient" of the male guinea pig liver was 40.2 and significantly different from the control group, but study authors did not specify the meaning of this term. Study authors also reported a dose-response relationship in the increased incidence of fatty degeneration of the liver. This fatty degeneration of the liver is given once in the report, apparently as a total incidence for control and increasing exposures (0/25, 0/22, 2/26, 4/25 and 7/22), and then again as "significant" at 2.5 mg/kg-day (1/26), 25 mg/kg-day (2/25), and 250 mg/kg-day (5/22). Likewise, shrinkage of splenic white pulp was noted in these "significant" liver exposure groups: 2/26 at 2.5 mg/kg-day, 2/25 at 25 mg/kg-day, and 7/22 at 250 mg/k-day. (See Table B.13). Based on these reported histopathological results, a NOAEL of 0.25 mg/kg-day and a LOAEL of 2.5 mg/kg-day is designated.

Developmental Study

Zhu et al. (1987d)

Zhu et al. (1987d) conducted a developmental toxicity study where female Chinese Keunming mice were orally administered sulfolane (purity not reported) in distilled water vehicle at dose levels of 0, 93, 280, or 840 mg/kg-day on Gestational Days (GD) 6–15. A positive control (N',N-methylene-bis-2-amino-5-sulfhydryl-1,3,4-thiadianole) and negative

control (distilled water) were also administered to pregnant mice. On GD 18, fetuses were removed and bodies, organs, and skeletons were examined for abnormalities. The study authors provided no other experimental details or methods of statistical analysis. Study authors reported that the incidence of skeletal abnormalities in the highest dose group (840 mg/kg-day) was significantly higher ($p < 0.01$, statistical test not reported) than the negative control. Study authors also stated that the number of fetal resorptions at the highest dose was greater than that of the negative control (30.16% versus 13.53%, respectively), but statistical significance was not specified. There were no skeletal abnormalities observed in pups in the 280 mg/kg-day group. Study authors did not state a NOAEL or LOAEL; however, data from the study indicate a maternal and developmental NOAEL of 280 mg/kg-day and corresponding LOAEL of 840 mg/kg-day. Although study authors did not indicate whether GLP was followed, the study is considered acceptable because both skeletal and visceral observations of the pups were made, and abnormalities in pups were detected after treatment with sulfolane.

Reproductive Study

Ministry of Health and Welfare Japan (1999)

The Ministry of Health and Welfare Japan (1999) conducted a one-generation reproductive/developmental toxicity screening test that was peer-reviewed by OECD (2004). The study report is written in Japanese but is summarized here based on secondary information from OECD (2004). Additionally, the data tables in the Ministry of Health and Welfare Japan study report are available in English. The study followed OECD 421 guidelines and was conducted under GLP standards. Study authors administered sulfolane (purity unreported) in water by gavage to 10-week-old Crj:CD(S-D) rats (12/sex/group) at doses of 0, 60, 200, or 700 mg/kg-day for 41−50 days. The dosing period extended from 14 days before mating to Lactation Day 3. Males and females were cohoused at a ratio of 1:1 for 14 days until proof of copulation. Clinical observations for general appearance were conducted twice per day for the parental generation and once per day for pups. During the mating period, body weight and food consumption were measured twice per week and then once per week in females during the gestation and lactation period. Estrous cycle was monitored daily until successful copulation. Study authors recorded the following parameters: number of successful copulated pairs, copulation index, paring days until copulation, number of pregnant females, fertility index, number of corpora lutea, number of implantation sites, implantation index, number of living

pregnant females, number of pregnant females with parturition, gestation length, number of pregnant females with live pups on Day 0, gestation index, number of pregnant females with live pups on Day 4, delivery index, number of pups alive on Day 0 of lactation, live birth index, sex ratio, number of pups alive on Day 4 of lactation, viability index, and bodyweight of live pups (on Days 0 and 4). At necropsy, study authors collected organ weights in the parental generation for testes, epididymides, and ovaries. Microscopic examinations of these organs were conducted for animals in the high-dose group only. Pups were examined macroscopically but apparently did not include a detailed organ or skeletal examination.

One high-dose male and one high-dose female died during the treatment period. High-dose animals of both sexes experienced decreased body weight gain and food consumption during premating (see Tables B.14 and B.15). Study authors also reported soiled fur, diarrhea, and soft stool in males at the 700 mg/kg-day dose group. In females of the 700 mg/kg-day dose group, study authors observed soiled fur during premating and increased relative ovary weight at necropsy (see Table B.16). Females dosed with 700 mg/kg-day had fewer estrous cycles, and four dams from this group experienced total litter loss during lactation (see Table B.17). The high-dose female group also experienced significantly decreased ($p < 0.01$) birth index, live index, and number of pups (on Lactation Days 1 and 4). The number of stillbirths was also significantly increased ($p < 0.01$) in this group. Furthermore, the females dosed with 200 mg/kg-day had significantly ($p < 0.05$) decreased delivery and birth indices (see Table B.18). Mean pup weight was significantly decreased on Lactation Days 0 the 700 mg/kg-day group ($p < 0.01$) (see Table B.19). At necropsy, study authors did not observe external anomalies in any of the treated pups. Authors established a NOAEL of 60 mg/kg-day for reproductive and developmental toxicity based on decreased delivery and birth index. The LOAEL is 200 mg/kg-day. OECD established a NOAEL of 700 mg/kg-day for male reproductive performance and a NOAEL of 200 mg/kg-day for female reproductive performance.

Limitations of the study report include lack of individual body weight, food consumption, uterine weight, and ovarian follicle counts data. Female estrous cycles were counted for 14 days prior to mating, but authors did not report measures of cycle length. Although male rats were

examined for reproductive organ atrophy and sperm count, sperm motility and morphology were not measured by study authors.

Carcinogenicity Studies

No studies pertaining to carcinogenicity of sulfolane to animals via oral exposure route are identified in the literature.

Inhalation Exposures

The effects of inhalation exposure of animals to sulfolane have been evaluated in one subchronic study testing multiple species (Andersen et al., 1977). No chronic, developmental, reproductive, or carcinogenicity studies via inhalation exposures have been identified in the literature.

Subchronic Study

Andersen et al. (1977)

In a published, peer-reviewed study, Andersen et al. (1977) conducted a series of tests investigating the subchronic inhalation toxicity of sulfolane to rats, guinea pigs, dogs, and squirrel monkeys. For the subchronic studies, both repeated and continual-exposure regimens were implemented by study authors. The methods and results for each exposure group, species, and dosing regimens were not clearly reported. For the sake of clarity, the study is divided into eight separate summaries (Andersen et al., 1977a–h) based on species and exposure regimen (repeated versus continual). The citation and associated experimental design for the subchronic studies are summarized in Table 3. Particle measurements given in the report, "a mean particle size between 1–4 microns in diameter" are sufficient to validate the study by indicating that the material could be breathed into the respiratory tract. This information is, however, not sufficient to perform more formal dosimetry that requires a measurement of mass median aerodynamic diameter (MMAD) and the variability, the sigma g, about that MMAD; therefore, formal dosimetry conversion to HEC for respiratory and extrarespiratory effects is not conducted for this study. Exposure concentrations are duration adjusted from intermittent exposure to continuous exposure 24 hours/day, 7 days/week ($CONC_{adj} = CONC_{study}$ [in mg/m^3] × [Hours per Day Exposed ÷ 24] × [Days Exposed ÷ Total Study Days]).

Table 3. Study Design and Citations for Andersen et al. (1977) Subchronic Inhalation Studies

Citation	Species and exposure regimen
Andersen et al., 1977a	Rat, repeated exposure, 8 hr/d, 5 d/wk
Andersen et al., 1977b	Rat, continual exposure, 23 hr/d, 7 d/wk
Andersen et al., 1977c	Guinea pig, repeated exposure, 8 hr/d, 5 d/wk
Andersen et al., 1977d	Guinea pig, continual exposure, 23 hr/d, 7 d/wk
Andersen et al., 1977e	Dog, repeated exposure, 8 hr/d, 5 d/wk
Andersen et al., 1977f	Dog, continual exposure, 23 hr/d, 7 d/wk
Andersen et al., 1977g	Monkey, repeated exposure, 8 hr/d, 5 d/wk
Andersen et al., 1977h	Monkey, continual exposure, 23 hr/d, 7 d/wk

For the various exposure regimens, study authors concluded that 20 mg/m^3 (19.2 mg/m^3 adjusted for continuous exposure) was the no-effect level for the four species of animals tested (rats, guinea pigs, dogs, and squirrel monkeys). However, for this review, a NOAEL and LOAEL are established for each species and exposure regimen.

Andersen et al. (1977a)

Andersen et al. (1977a) exposed 8 male and 7 female Sprague-Dawley rats via whole-body inhalation exposure to a concentration of 495 ± 75 mg/m^3 (mean ± standard deviation) aerosolized sulfolane-W (sulfolane plus 3% water to prevent freezing, purity unreported) for 8 hours/day, 5 days/week, for 27 exposure days over a total study duration of 37 days. It is unclear from the study report whether a separate, untreated control group was tested. Study authors indicate changes "compared to controls" in the text; however, the use of an untreated control group was not stated in the experimental design. Adjusted daily concentration calculated for a total study duration of 37 days (includes weekends) over 24 hours/day, 7 days/week is 120 mg/m^3. Test concentrations within chambers were determined by chromatographic analysis at 6-hour intervals. Rats were housed in Rochester-type chambers with sulfolane reservoirs, and input lines were wrapped in heat tape and maintained above room temperature to prevent freezing. Airflow through the chambers was maintained at 1 m^3/min. Dry chow (unreported brand) and water were provided ad libitum. Authors did not report if the study was conducted according to GLP standards.

Authors determined body weights, total and differential leukocyte counts, hemoglobin concentrations, and hematocrit levels prior to and following exposure. The timepoint of postexposure sampling for the repeat-dose study is not clearly stated in the study report. Additional analyses performed after exposure included creatinine and urea nitrogen levels, cholesterol, lactate dehydrogenase (LDH), AST, ALT, and ALP activity. Rats were observed at unreported intervals for clinical signs of toxicity and abnormal behavior. Authors collected 24-hour urine samples and recorded pH, protein, sugar, ketone bodies, and occult blood. Histopathological analysis was performed on tissues from the lung, bronchus, heart, kidney, bile duct, liver, spleen, stomach, intestine, pancreas, cerebellum, esophagus, thyroid, trachea, lymph node, bladder, and aorta of an unreported number of animals. Authors used Student's *t*-test to compare preexposure and postexposure levels ($p < 0.05$).

Andersen et al. (1977a) observed no mortalities or significant differences in hematology or body weight between preexposure and postexposure levels. A small, statistically nonsignificant decrease in white blood cell count in sulfolane-treated rats versus control was reported; however, specific values were not reported. Authors observed chronic lung inflammation in all animals but provided no information regarding severity. Study authors reported chronic liver inflammation in 1/5 males and 3/3 females; however, they did not address the inconsistencies between the number of animals reported in each dose group ($n = 8$ males, 7 females) and the number of animals examined for pathology ($n = 5$ males, 3 females). Authors concluded that sulfolane vapor is not toxic to rats under these experimental conditions. Based on chronic lung and liver inflammation observed in rats at the only concentration tested, a LOAEL of 120 mg/m^3 is established.

Andersen et al. (1977b)

Andersen et al. (1977b) administered sulfolane by whole-body inhalation exposure to Sprague-Dawley rats at concentrations of 2.8 ± 1.4 mg/m^3 for 90 days ($n = 15$ males), 4.0 ± 1.0 mg/m^3 for 110 days ($n = 15$ males), or 20 ± 6.7 mg/m^3 for 95 days ($n = 8$ males, 7 females) for 23 hours/day, 7 days/week. Adjusted daily concentrations calculated for continuous exposure over 24 hours/day, 7 days/week are 2.7, 3.8, and 19.2 mg/m^3. No control group was examined for this study. The test substance used, the method of test concentration

determination, and animal husbandry are as reported in Andersen et al. (1977a). Authors did not report if this study was conducted in compliance with GLP standards.

Animals were weighed and blood drawn for analysis prior to exposure, after 30 exposure days, after 60 exposure days, and "at the end of exposure." The exact time interval for postexposure examination is unclear. Authors examined all endpoints reported in Andersen et al. (1977a) and used Student's *t*-test to compare preexposure and postexposure data.

Andersen et al. (1977b) reported no mortalities or significant changes in hematology, biochemistry, or body weight between preexposure and postexposure observations. One rat (sex not reported) at the 19.2 mg/m^3 concentration was observed to have a small circumscribed peripheral liver lesion, and 2/7 females at the same exposure had slightly elevated AST, ALT, and LDH activity levels. Authors reported that the liver lesion was not considered to be related to sulfolane exposure, and the dose-related nature of the clinical chemistry observations was unclear. A NOAEL of 19.2 mg/m^3 is established. This NOAEL is the highest concentration tested in the study that had no observed adverse effects at all concentrations.

Andersen et al. (1977c)

Andersen et al. (1977c) also exposed 8 male and 7 female Hartley-derived guinea pigs to a concentration of 495 ± 75 mg/m^3 sulfolane by whole-body inhalation exposure for 8 hours/day, 5 days/week, for 27 exposure days. The test chemical used is described in Andersen et al. (1977a). Adjusted daily concentration calculated for a total study duration of 37 days (includes weekends) and 24-hour treatment is 120 mg/m^3. It is unclear if an untreated control group was used in this study. Determination of test concentrations within chambers and husbandry are as described in Andersen et al. (1977a).

Study authors weighed animals and examined hematology prior to exposure. Total and differential leukocyte counts, hemoglobin concentrations, and hematocrit were determined and re-evaluated after exposure (exact time interval for postexposure examination is unclear). Endpoints examined are those reported in Andersen et al. (1977a).

Andersen et al. (1977c) reported no significant differences in preexposure and postexposure body weight, hematology, or biochemistry. Preexposure and postexposure white blood cell, hematocrit, and hemoglobin counts are reported in Table B.20. Although a control group is reported in this table, authors do not mention an untreated group, and it is unclear what this "control" group represents. Authors reported that some degree of chronic lung inflammation (incidence and severity unreported) was observed in all animals. Authors concluded that sulfolane vapor is not toxic to guinea pigs under these experimental conditions. Based on lung inflammation in guinea pigs, a LOAEL of 120 mg/m^3 is established. The LOAEL represents the only dose tested in this experiment.

Andersen et al. (1977d)

Andersen et al. (1977d) exposed Hartley-derived guinea pigs via whole-body inhalation to sulfolane at concentrations of 2.8 ± 1.4 mg/m^3 for 90 days (n = 15 males), 4.0 ± 1.0 mg/m^3 for 110 days (n = 15 males), 20 ± 6.7 mg/m^3 for 95 days (n = 8 males, 7 females), 159 ± 68 mg/m^3 for 85 days (n = 24 males, 24 females), or 200 ± 48 mg/m^3 for 90 days (n = 15 males, 15 females) exposure for 23 hours/day, 7 days/week. The test chemical used is described in Andersen et al. (1977a). Adjusted daily concentrations calculated for continuous exposure over 24 hours/day, 7 days/week are 2.7, 3.8, 19.2, 152, and 192 mg/m^3, respectively. It is unclear if an untreated control group was used in this study. Some data tables within the study report indicate a control group, but study authors do not explicitly mention this group in the methods section. Determination of test concentrations within chambers and husbandry are as described in Andersen et al. (1977a).

Study authors weighed animals and drew blood for analysis prior to exposure, after 30 exposure days, after 60 exposure days, and "following exposure" (Andersen et al., 1977d). The exact time interval of postexposure examination is unclear. Guinea pigs (exact number unreported) in the 152 mg/m^3 exposure-group were also bled from the toe at 10-day intervals. Authors report that in the 192 mg/m^3 exposure group, 8 males and 2 females were bled after 20 exposure-days and that 5 males and 5 females were removed at 30 and 60 exposure-days for examination of body weight, hematology, biochemistry, and necropsy. Tissues from half of these animals were histopathologically examined. Authors examined all endpoints reported

previously (Andersen et al., 1977a) and used Student's *t*-test to compare preexposure and postexposure data.

Authors reported no mortalities, signs of clinical toxicity, or changes in body weight, hematology, biochemistry, or treatment-related pathology at exposures ≤152 mg/m^3. In the 19.2 mg/m^3 exposure group, study authors observed pale livers that they did not consider related to sulfolane treatment, but they did not provide details regarding incidence or severity of the effect.

Authors reported significantly decreased white blood cell count in the highest exposure group (192 mg/m^3) compared to preexposure levels on Days 20, 30, and 90 but not Day 60 (see Table B.21). However, the data table provided by study authors includes an untreated control group that is not mentioned in their explanation of methods, and it is unclear what this "control" group represents. The white blood cell count data are not amenable to benchmark dose modeling because the number of animals in each exposure group was not clearly stated. No significant changes in body weight or enzyme activity levels were observed at the 192 mg/m^3 level, although slight, nonsignificant increases in plasma AST and ALT activities were observed at 30 and 60 days. No significant changes in hematocrit or hemoglobin counts were observed at any postexposure sampling period at the 152 or 192 mg/m^3 groups. Chronic pleuritis was observed in all 10 guinea pigs in the 192 mg/m^3 group necropsied at 30 days. Authors reported fatty vacuolization in 4/5 guinea pig livers at 30 days, 6/7 at 60 days, and 4/5 at 90 days; however, the inconsistencies between the number of animals reported to be necropsied previously in the study (0 at 30 days, 5 of each sex at 60 and 90 days) and those reported to be observed (5 at 30 days, 7 at 60 days, and 5 at 90 days) were not addressed. Based on chronic pleuritis, decreased white blood cell counts, and fatty vacuolation in liver of guinea pigs, a NOAEL of 152 mg/m^3 is established, with a corresponding LOAEL of 192 mg/m^3.

Andersen et al. (1977e)

Andersen et al. (1977e) also exposed two male Beagle dogs to a concentration of 495 ± 75 mg/m^3 sulfolane by whole-body inhalation exposure for 8 hours/day, 5 days/week, for 27 exposure days. The test chemical used is described in Andersen et al. (1977a). Adjusted daily concentrations calculated for a total study duration of 37 days (includes weekends) and

24 hours/day, 7 days/week is 120 mg/m^3. No untreated control group was used in this study. Determination of test concentrations within chambers and husbandry are as described previously (Andersen et al., 1977a).

Parameters examined in Andersen et al. (1977e) are as described in Andersen et al. (1977a) with the exception that urine samples were not collected. Authors observed no significant changes in body weight, hematology, biochemistry, or pathology. Chronic lung inflammation was observed in both animals (severity not reported). A LOAEL of 120 mg/m^3 is established based on chronic lung inflammation.

Andersen et al. (1977f)

The subchronic inhalation study (Andersen et al., 1977f) is selected as the principal study for derivation of the subchronic RfC and screening chronic RfC. Andersen et al. (1977f) exposed male beagle dogs to concentrations of 2.8 ± 1.4 mg/m^3 sulfolane for 90 days (n = 1), 4.0 ± 1.0 mg/m^3 for 110 days (n = 1), 20 ± 6.7 mg/m^3 for 95 days (n = 2), or 200 ± 48 mg/m^3 for 90 days (n = 4) by whole-body inhalation exposure for 23 hours/day, 7 days/week. Adjusted daily concentrations calculated for continuous treatment over 24 hours/day, 7 days/week are 2.7, 3.8, 19.2, and 192 mg/m^3, respectively. The test chemical used is described in Andersen et al. (1977a). No untreated control group was used in this study. Determination of test concentrations within chambers and husbandry methods are described previously (Andersen et al., 1977a).

Authors examined parameters previously detailed in Andersen et al. (1977a) with the exception that urine samples were not collected. Authors observed no mortalities, signs of clinical toxicity, changes in body weight, hematology, biochemistry, or pathology for the three low-exposure levels (≤19.2 mg/m^3).

At the 192 mg/m^3 exposure-level, authors reported intermittent convulsions (incidence and severity not reported) and frequent displays of fiercely aggressive behavior both toward other dogs and their handlers. During periods of convulsive activity, authors noted episodic, slow, and labored breathing. Authors sacrificed one dog on exposure Day 11 after the animal experienced many severe generalized motor seizures. Another dog was sacrificed on exposure

Day 29 after he became so aggressive as to be considered a danger to the handlers. A third dog was removed from the testing chamber after 13 exposure-days due to dangerously aggressive behavior. After a 29-day recuperative period, the dog was returned to the testing chamber but died 7 days later (exposure Day 49) during a violent convulsion. The fourth dog was removed from the chamber on exposure Day 27 (specific reason not given), allowed to recuperate for 3 days, and survived the full 90 days. Gross pathologic evaluation showed that three of four dogs had pneumonia, and in two of these cases, histologic examination revealed chronically inflamed and hemorrhagic lungs. Authors concluded that these effects were probably due to a combination of pulmonary and nervous system toxicity. Clinical chemistry measurements taken at Day 60 revealed grossly elevated plasma AST, ALT, and LDH levels in one dog (360, 111, and 96 IU/L, respectively; study authors did not report values for an untreated control).

No effects were observed at the 19.2 mg/m^3 exposure level, while animals at the next-highest dose exhibited frank effects such as severe motor seizures, convulsions, and death. Based on information in the study, an FEL of 192 mg/m^3 and a NOAEL of 19.2 mg/m^3 are identified. The NOAEL is used as the point of departure for derivation of the subchronic and screening chronic p-RfC.

Andersen et al. (1977g)

Andersen et al. (1977g) also exposed nine male squirrel monkeys (*Saimiri sciureus*) to a concentration of 495 ± 75 mg/m^3 sulfolane by whole-body inhalation exposure for 8 hours/day, 5 days/week, for 27 exposure days. The test chemical used is described in Andersen et al. (1977a). Adjusted daily concentration calculated for a total study duration of 37 days (includes weekends) and continuous exposure 24 hours/day, 7 days/week is 120 mg/m^3. No untreated control group was used in this study. Determination of test concentrations within chambers and husbandry are described previously (Andersen et al., 1977a).

Parameters examined by Andersen et al. (1977g) are as described previously (Andersen et al., 1977a) with the exception that urine samples were not collected. Three animals died, one each on Days 7, 9, and 15. Five others were sacrificed in extremis between Days 9 and 17. Authors noted blood tinged fluid around the eyes (incidence and severity not reported). Pathology revealed pale livers and hearts (incidence and severity not reported), and authors

reported 5/6 monkeys had fatty metamorphosis of the liver. Authors also reported a slight, statistically nonsignificant decrease in white blood cell count and some degree of chronic lung inflammation in all animals (severity not reported). Based on mortality observed at the only concentration tested, an FEL of 120 mg/m^3 is established.

Andersen et al. (1977h)

Andersen et al. (1977h) exposed male squirrel monkeys (*Saimiri sciureus*) to concentrations of 2.8 ± 1.4 mg/m^3 sulfolane for 90 days (n = 9), 4.0 ± 1.0 mg/m^3 for 110 days (n = 9), 20 ± 6.7 mg/m^3 for 95 days (n = 6), or 200 ± 48 mg/m^3 for 90 days (n = 2) by whole-body inhalation exposure for 23 hours/day, 7 days/week. The test chemical used is described in Andersen et al. (1977a). Adjusted daily concentrations calculated for continuous exposure over 24 hours/day, 7 days/week are 2.7, 3.8, 19.2, and 192 mg/m^3, respectively. No untreated control group was used in this study. Determination of test concentrations within chambers and husbandry are as described in Andersen et al. (1977a).

Authors examined parameters detailed in Andersen et al. (1977a) with the exception that urine samples were not collected. Authors observed no mortalities, signs of clinical toxicity, changes in body weight, hematology, biochemistry, or pathology for the three low exposure levels (≤19.2 mg/m^3). At the 192 mg/m^3 exposure level, one animal died on Day 3, and the other was sacrificed in a moribund state on Day 4. Authors reported that both animals were heavily infested with parasites and that this could have contributed to their susceptibility. Authors also noted that the monkey sacrificed on Day 4 had chronic pleuritis. No other information was provided. In this exposure regimen, an FEL (death) of 192 mg/m^3 and a NOAEL of 19.2 mg/m^3 is identified.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

The database of other experiments on sulfolane includes genotoxicity, effects on thermoregulation, toxicokinetics, and neurotoxicity. The genotoxicity studies are summarized in Table 4A while other studies are summarized in Table 4B.

Table 4A. Summary of Sulfolane Genotoxicity

Endpoint	Test System	Dose/ Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in prokaryotic organisms						
Reverse mutation	*S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 *E. coli* WP2, WP2uvrA	0–52,000 µg/plate	–	–	No precipitation at any concentration with or without S9	Ministry of Health and Welfare Japan (1996b) as reported in OECD (2004); Shell Oil Company (1982) ; Phillips Petroleum Co. (1984); Zhu et al. (1987e)
SOS repair induction	ND					
Genotoxicity studies in nonmammalian eukaryotic organisms						
Mutation	*S. cerevisiae*	0–5 mg/mL	–	–		Shell Oil Company (1982)
Recombination induction	ND					
Chromosomal aberration	ND					
Chromosomal malsegregation	ND					
Mitotic arrest	ND					
Genotoxicity studies in mammalian cells—in vitro						
Mutation	Mouse lymphoma L5178Y TK cells	0–1000 µg/mL	+	+	Considered positive by study authors but no dose-response observed.	Phillips Petroleum Co. (1984); also reported in OECD (2004), however OECD cites study as "Phillips Petroleum Co. (1982)"
Chromosomal aberrations	Chinese hamster CHL/IU	0, 0.3, 0.6, or 1.2 mg/mL	–	–	No structural aberrations/polypoidy induced in continuous (24 or 48 hr) or short-term (6 hr) treatment	Ministry of Health and Welfare Japan (1996c) as reported in OECD (2004)
Chromosomal aberrations	Rat liver, RL4 cells	0–1000 µg/mL	–	NA		Shell Oil Company (1982)

Table 4A. Summary of Sulfolane Genotoxicity

Endpoint	Test System	Dose/ Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Sister chromatid exchange (SCE)	Chinese hamster ovary cells	0–6400 µg/mL	–	–	Growth inhibition at 6400 µg/mL	Phillips Petroleum Co. (1984)
Sister chromatid exchange (SCE)	Human peripheral lymphocytes	0, 0.01, 0.1, 1, 10 mg/mL	–	NR	Growth inhibition at 10 mg/mL	Zhu et al. (1987e)
DNA damage	ND					
DNA adducts	ND					
Genotoxicity studies in mammals—in vivo						
Mouse bone marrow micronucleus test	7-wk-old mouse (strain, sex not specified); orally administered sulfolane	62.5, 125, 250, 500, 1000 mg/kg	–			Zhu et al. (1987e)
Chromosomal aberrations	ND					
Sister chromatid exchange (SCE)	ND					
DNA damage	ND					
DNA adducts	ND					
Mouse biochemical or visible specific locus test	ND					
Dominant lethal	ND					
Genotoxicity studies in subcellular systems						
DNA binding	ND					

[a]Lowest effective dose for positive results, highest dose tested for negative results.
[b]+ = positive, ± = equivocal or weakly positive, – = negative, T = cytotoxicity, NA = not applicable, ND = no data, NDr = Not determined, NR = Not reported, NR/Dr = Not reported by the study author, but determined from data.

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Carcinogenicity other than oral/inhalation	ND			
Short-term studies	ND			
Metabolism/ toxicokinetics	Male Wistar rat, female rabbit (species unspecified); 100 mg in 2 mL water i.p. injection;	One major metabolite identified (3-hydroxysulfone); metabolite comprised 85% of urinary radioactivity.	Sulfolane is excreted mainly through urine after i.p. injection.	Roberts and Warwick (1961)
Metabolism/ toxicokinetics	Rat, 500 and 1000 mg/kg i.v.	Sulfolane was excreted unchanged in urine; percentage of dose excreted unchanged in the urine was >50% between Days 0 and 2 at 1000 mg/kg; plasma half-life was 3.5–5 hr.	Sulfolane was rapidly distributed in rat after i.v. administration.	Andersen et al. (1976)
Metabolism/ toxicokinetics	12 Sprague-Dawley (S-D) rat, 0.2 mL [^{3}H]-sulfolane (95.3% radiochemical purity, 1.733 mCi/mg specific radioactivity) injected into ligated sections of GI tract 55 S-D rat, oral dose (40uCi/100g bodyweight), blood and organs weighed and measured for distribution pregnant S-D rat (number unspecified) killed 2 hr after administration and examined for distribution to embryo 3 male S-D rat, biliary tract plunging tubes collected bile every 10 min within 72 hr after oral dose of [^{3}H]-sulfolane	Major absorption site was small intestine, half life for absorption is 0.15 hr; T_{max} (time to maximum plasma concentration) is 1.16 hr; [^{3}H]-sulfolane present in every organ with peak levels at 1 hr, decreasing thereafter; at the peak, levels highest in liver, followed by the kidney and lung; elimination half life of [^{3}H]-sulfolane was longest in brain tissue (31.22 ± 4.68 d); blood concentration in embryos mirrored pregnant dams, while the placenta had a higher concentration; biliary excretion only 3% of administrated dose after 72 hr; excretion in urine and feces accounted for 31 and 15% of administered dose, respectively; kinetic constant for sulfolane is 4.47 hr^{-1}	Sulfolane is rapidly and completely absorbed and distributed throughout the body; excretion occurs mainly through the urine, with some excretion through the feces.	Zhu et al. (1988)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
	5 male S-D rat, oral doses, urine and feces collected every 10 min for 72 hr			
Mode of action/ mechanistic	ND			
Immunotoxicity	ND			
Neurotoxicity	Male S-D-derived rat, Hartley derived guinea pig, New Zealand white rabbit, and Swiss albino mouse; doses administered i.v., orally, i.p, and s.c. (exact doses not provided). LD_{50} values calculated from mortality after 1-wk observation.	Hunched posture, increased auditory sensitivity, hyperreactivity, and rapid respiration in rats and mice; at lethal doses, all species experienced clonic-tonic convulsions; LD_{50} values determined for i.v. administration were approximately half the value of those for i.p., oral, and subcutaneous administrations for all species.	Authors concluded that sulfolane has an excitatory effect on the central nervous system following acute administration.	Andersen et al. (1976)
Neurotoxicity	Male S-D rat; single i.p. injection of either saline or 200, 400, or 800 mg/kg-bw; body temperature and metabolic rate were recorded at ambient temperatures of 15°C, 25°C, or 35°C.	No effect of sulfolane at 35°C; at lower ambient temperature, hypothermia and hypometabolism were induced by sulfolane in the rat.	Authors concluded that "hypometabolic and hypothermic efficacy of sulfolane is dependent on ambient temperature."	Gordon et al. (1984)
Neurotoxicity	Male S-D rat; single i.p. injection of either saline or 800 mg/kg; metabolic rate, tail skin temperature, colonic (deep body) temperature, and preferred body temperature were recorded at ambient temperatures of 15°C or 25°C.	Sulfolane reduced metabolic rate and colonic temperature at both ambient temperatures tested; preferred ambient temperature and tail skin temperature unaffected by treatment.	Authors concluded sulfolane toxicity is greater at increased ambient temperatures.	Gordon et al. (1985)
Neurotoxicity	Male Long-Evans hooded rat;	Hypothermia at doses ≥400 mg/kg-bw	Authors concluded that increasing ambient	Ruppert and Dyer

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
	single i.p. injection of either saline or 200, 400, or 800 mg/kg-bw; body temperature and motor activity were measured at ambient temperatures of 20.8°C or 32.3°C.	at 20.8°C; hypothermia attenuated at 32.3°C; at both temperatures, motor activity decreased at doses ≥400 mg/kg-bw.	temperature attenuates hypothermia in sulfolane-treated rats, but sulfolane-induced hypoactivity was still evident when tested at both the higher and lower ambient temperatures.	(1985)
Neurotoxicity	Male Long-Evans hooded rat; single i.p. injection of either saline or 200, 400, or 800 mg/kg-bw sulfolane; visual evoked potentials (VEP) were measured by surgically-implanted electrodes.	No clinical changes in behavior; dose-dependent increase in latency of visual evoked potentials (statistically significant at ≥400 mg/kg-bw); dose-dependent hypothermia.	Authors concluded that acute administration of sulfolane produced clear alterations of visual system function and hypothermia. However, when hypothermia was attenuated by increasing ambient temperature, VEP latencies diminished, indicating that latencies were likely secondary to sulfolane-induced hypothermia.	Dyer et al. (1986)
Neurotoxicity	Male CD-1 mouse; single i.p. injection of saline or 200, 400, 600, or 800 mg/kg sulfolane in volume of 0.3 mL/100 g bw; Experiment 1 measured preferred ambient temperature immediately following injection; Experiment 2 measured metabolic rate and colonic temperature at ambient temperatures of 20°C, 30°C, or 35°C immediately following injection.	Sulfolane-treated mice had significantly lower metabolic rate and body temperature at lower ambient temperatures (<30°C). Mice exhibited behavioral preference for lower ambient temperature after treatment with sulfolane. Percent mortality after a LD_{50} dose of sulfolane increased with increasing ambient temperature.	Authors concluded that sulfolane-treated mice exhibited both autonomic and behavioral decrease in body temperature in order to reduce toxic effects of sulfolane.	Gordon et al. (1986)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Neurotoxicity	Male Long-Evans hooded rat; single i.p. injection of saline or 200, 400, or 800 mg/kg; Experiment 1 measured presence of audiogenic (AG) seizures and potentiation of pentylenetetrazol (PTZ) seizures; second and third experiments measured effect of body temperature on seizure occurrence using 400 and 800 mg/kg groups (Experiment 2) and the 800 mg/kg group (Experiment 3)	AG seizures occurred in half of the high-dose animals in first two experiments; sulfolane-induced hypothermia showed a protective effect and reduced AG seizure characteristics; doses of 800 mg/kg increased PTZ seizure severity and at 400 and 800 mg/kg, seizure duration was significantly increased; AD seizure activity was not affected significantly by treatment	Doses of 800 mg/kg sensitized typically resistant rats to AG seizures and increased severity and duration of PTZ seizures; the data suggest that sulfolane treatment does not significantly affect the hippocampus.	Burdette and Dyer (1986)
Neurotoxicity	Male New Zealand White rabbit; single injection of 100, 300, or 1000 µg sulfolane in a 3-µL volume of saline directly into preoptic/anterior hypothalamic (POAH) area via stereotaxically implanted cannula; single injection of 300, 100, or 3000 µg in a 3-µL volume of saline directly into intracerebrovenricular (ICV) area; POAH temperature, ear temperature, and metabolic rate were measured.	No statistically significant thermoregulatory effects upon direct injection into POAH; however, significant hyperthermia observed at 60–120 min postdosing upon injection into the ICV at 3000 µg.	Study authors concluded that sulfolane did not directly act on the thermoregulatory neurons of the CNS since no changes in temperature were observed when injected directly into the POAH. This finding contrasts previous findings of systemic (i.p.) injection of sulfolane where hypothermia was induced.	Mohler and Gordon (1989)

Tests Evaluating Carcinogenicity, Genotoxicity, and/or Mutagenicity

The genotoxicity of sulfolane has been evaluated in bacterial and eukaryotic in vitro systems and has yielded predominantly negative results. In bacterial cells, sulfolane was negative for inducing reverse mutations in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and *E. coli* strains WP2 and WP2uvrA at concentrations up to 52,000 µg/plate, with or without metabolic activation (±S9). Study authors reported that no test compound precipitation or cytotoxicity occurred at concentrations up to 52,000 µg/plate. The only positive result for genotoxicity was reported in an unpublished mouse lymphoma assay by Phillips Petroleum Co. (1984) where study authors exposed L5178Y cells ($T/K^{+/-}$) to sulfolane at concentrations of 60, 90, 135, 202, 301, 449, 670, or 1000 µg/mL; however, OECD (2004) noted that there was no dose response observed, and the survival percentage was not affected by increasing doses. Therefore, OECD considered the positive result as an incorrect interpretation by Phillips Petroleum Co. (1984). Sulfolane was negative for inducing mutations in a nonmammalian eukaryotic test system (*S. cerevisae*) at concentrations up to 5 mg/mL (±S9) and negative for inducing chromosomal aberrations in Chinese hamster CHL/IU and rat liver RL4 cells. Sulfolane did not induce sister chromatid exchange in Chinese hamster ovary cells at concentrations up to 6400 µg/mL.

Other Toxicity Studies (Exposures Other Than Oral or Inhalation)

Information is not available in this regard.

Short-term studies

Information is not available in this regard.

Metabolism/toxicokinetic Studies

Zhu et al. (1988), Roberts and Warwick (1961), and Andersen et al. (1976) provide information on the toxicokinetics and metabolism of sulfolane. Data indicate that sulfolane is rapidly and completely absorbed and distributed throughout the body when dosed orally, i.p., or i.v., and excretion occurs mainly through the urine. Further information is provided in Table 4B.

Mode of Action/mechanistic

Information is not available in this regard.

Immunotoxicity

Information is not available in this regard.

Neurotoxicity

Sulfolane has been shown to elicit changes in thermoregulation of experimental animals. Overall, study authors observed that sulfolane-treated rodents demonstrated increased survivability at lower ambient temperatures. The various studies are presented in Table 4B.

DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present a summary of noncancer and cancer reference values, respectively. IRIS data are indicated in the table, if available.

Table 5. Summary of Reference Values for Sulfolane (CASRN 126-33-0)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Screening subchronic p-RfD (mg/kg-d)	Rat/F	Decreased total and differential white blood cell counts (lymphocytes, basophils, monocytes, and LUC)	1×10^{-2}	NOAEL	2.9	300	Huntingdon Life Sciences (2001)
Screening chronic p-RfD (mg/kg-d)	Rat/F	Decreased total and differential white blood cell counts (lymphocytes, basophils, monocytes, and LUC)	1×10^{-3}	NOAEL	2.9	3000	Huntingdon Life Sciences (2001)
Subchronic p-RfC (mg/m^3)	Dog/M	Chronically inflamed and hemorrhagic lungs; neurological effects	2×10^{-2}	NOAEL	19.2	1000	Andersen et al. (1977f)
Screening chronic p-RfC (mg/m^3)	Dog/M	Chronically inflamed and hemorrhagic lungs; neurological effects	2×10^{-3}	NOAEL	19.2	10,000	Andersen et al. (1977f)

1

Table 6. Summary of Cancer Values for Sulfolane (CASRN 126-33-0)				
Toxicity Type	**Species/Sex**	**Tumor Type**	**Cancer Value**	**Principal Study**
p-OSF	None	None	None	None
p-IUR	None	None	None	None

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

No subchronic p-RfD value can be derived for the following reason: no adequate, well-described studies are available in the published literature.

Justification

Based on the available literature, the most acceptable study to derive an oral reference value is an unpublished study (Huntingdon Life Sciences, 2001) that identified reduced white blood cell counts in female rats exposed to sulfolane in drinking water for 13 weeks. Although alternative published, peer-reviewed studies are available (Ministry of Health and Welfare Japan, 1996a; Zhu et al., 1987), these reports are originally published in a foreign language (Japanese and Chinese, respectively), and the provided translations do not contain detailed documentation of experimental methods and study design. The 28-day repeated dose study performed by the Ministry of Health and Welfare Japan (1996a) was reviewed and translated by OECD (2004), but OECD did not provide husbandry data and did not explicitly list the pathology parameters examined. In the translation of the Zhu et al. (1987) paper, information is not provided on the type or frequency of oral exposure, strain of animals used, specific biochemical parameters examined, specific organs examined, type of pathology examined, or methods for statistical analysis. It is unknown whether Zhu et al. (1987) followed GLP guidelines. The methods in the Huntingdon Life Sciences study are well-documented, and the study adheres to GLP standards. Additionally, the study authors conducted the drinking water study at a lower dose range and examined a wider array of endpoints than the available published studies, and thus, the unpublished study was able to detect more sensitive effects of sulfolane. Nevertheless, the fact that it is an unpublished study precludes its use for this purpose at this time. This study however, is currently being externally peer-reviewed by independent experts, which would allow it's use in the derivation of a provisional subchronic RfD if the study is deemed acceptable by the peer-reviewers.

The GLP-compliant, unpublished subchronic study by Huntingdon Life Sciences (2001) is therefore selected to derive a screening subchronic p-RfD. Discussion on the derivation of the screening subchronic p-RfD is available in Appendix A.

Derivation of Chronic Provisional RfD (Chronic p-RfD)

No chronic p-RfD value can be derived for the following reason: no adequate, well-described studies are available.

Justification

The only available chronic oral study is a published foreign study by Zhu et al. (1987) who exposed guinea pigs to sulfolane by oral administration for 6 months. As stated previously, the study translation does not clearly state the experimental methods. It is unknown whether study authors followed GLP guidelines. Therefore, the GLP-compliant, unpublished study provided by Huntingdon Life Sciences (2001) is selected as the principal study to derive a screening chronic p-RfD. Discussion on the derivation of a screening chronic p-RfD is available in Appendix A.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of Subchronic Provisional RfC (Subchronic p-RfC)

The study by Andersen et al. (1977f) is selected as the principal study for the derivation of the subchronic p-RfC. The critical endpoint is chronically inflamed and hemorrhagic lungs and neurological effects in male beagle dogs. The study was conducted before GLP guidelines were instituted. Details of the study are provided in the "Review of Potentially Relevant Data" section. Other inhalation studies did not provide a lower POD or had improper animal husbandry. A rat study (Andersen et al., 1977b) had the same NOAEL but did not identify a LOAEL. The data is not amenable to benchmark dose modeling because there is no dose-response observed. The Anderson 1977f study represents the lowest POD for developing a subchronic p-RfC.

The POD in this study is an unadjusted NOAEL of 20 mg/m^3 as reported by the study authors. Dosimetric adjustments were performed for continuous duration. Conversion to HEC is not performed due to inadequate information (no MMAD determination) on aerosol particle size.

$$\begin{aligned} NOAEL_{ADJ} &= NOAEL \times (\text{Hours per Day Dosed} \div 24) \times (\text{Days Dosed} \div \text{Total Study Days}) \\ &= 20\ mg/m^3 \times (23 \div 24) \times (95\ \text{Days Dosed} \div 95\ \text{Total Study Days}) \\ &= 20 \times 0.958 \\ &= 19.2\ mg/m^3 \end{aligned}$$

Subchronic p-RfC = $NOAEL_{ADJ} \div UF$
= $19.2\ mg/m^3 \div 1000$
= $\mathbf{2 \times 10^{-2}\ mg/m^3}$

Table 7 summarizes the uncertainty factors for the subchronic p-RfC of sulfolane.

Table 7. Uncertainty Factors for Subchronic p-RfC of Sulfolane

UF	Value	Justification	Notes
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between dogs and humans.	Dosimetric conversion is not performed due to missing aerosol size information.
UF_D	10	A UF_D of 10 is selected because there are no acceptable two-generation reproduction studies or developmental studies via the inhalation route.	
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response to humans.	
UF_L	1	A UF_L of 1 is applied because a NOAEL was used.	
UF_S	1	A UF_S of 1 is applied because a subchronic study was utilized.	
UF_C ≤3000	1000		

The confidence of the subchronic p-RfC for sulfolane is low as explained in Table 8 below.

Table 8. Confidence Descriptors for Subchronic p-RfC for Sulfolane

Confidence Categories	Designation[a]	Discussion
Confidence in study	L	The study by Andersen et al. (1977) does not provide particle size information for subchronic studies and the methods are not clearly reported.
Confidence in database	L	The database for subchronic inhalation exposure includes the single study by Andersen et al. (1977).
Confidence in subchronic p-RfD[b]	L	

[a]L = Low, M = Medium, H = High.
[b]The overall confidence cannot be greater than lowest entry in table.

Derivation of Chronic Provisional RfC (Chronic p-RfC)

No chronic p-RfC can be derived for the following reason: the composite uncertainty factor for the chronic p-RfC is >3000. Therefore, the value is relegated to a screening-level value, and discussion for the derivation of a screening chronic p-RfC is available in Appendix A.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 9 identifies the cancer weight-of-evidence descriptor for sulfolane.

Table 9. Cancer WOE Descriptor for Sulfolane

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"		NA	
"Likely to Be Carcinogenic to Humans"		NA	
"Suggestive Evidence of Carcinogenic Potential"		NA	
"Inadequate Information to Assess Carcinogenic Potential"	**X**	**Both**	**No carcinogenicity studies on human or animal exposure to sulfolane via the oral or inhalation route are available in the literature.**
"Not Likely to Be Carcinogenic to Humans"		NA	

MODE OF ACTION DISCUSSION

The *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) define mode of action as a sequence of key events and processes starting with the interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation. Examples of possible modes of carcinogenic action include mutagenic, mitogenic, antiapoptotic

(inhibition of programmed cell death), cytotoxic with reparative cell proliferation, and immune suppression. Based on the available literature, sulfolane is negative for genotoxicity. Because there are no available studies on the carcinogenicity of sulfolane, the mode of action discussion is precluded.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor (p-OSF)

There are insufficient data to assess the carcinogenic potential of sulfolane via the oral route; therefore, derivation of a provisional oral slope factor is precluded.

Derivation of Provisional Inhalation Unit Risk (p-IUR)

There are insufficient data to assess the carcinogenic potential of sulfolane via the inhalation route; therefore, derivation of a provisional inhalation unit risk is precluded.

APPENDIX A. PROVISIONAL SCREENING VALUES

For the reasons noted in the main document, it is inappropriate to derive a provisional subchronic and chronic p-RfD and chronic p-RfC for sulfolane. However, information is available which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in a supplemental and develops a screening value. Appendices receive the same level of internal and external scientific peer review as the main document to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in a supplement to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of a supplement screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Heath Risk Technical Support Center.

DERIVATION OF SCREENING PROVISIONAL ORAL REFERENCES DOSES

Derivation of Screening Subchronic Provisional RfD (Subchronic p-RfD)

The unpublished study by Huntingdon Life Sciences (2001) is selected as the principal study for derivation of the screening subchronic p-RfD. The critical endpoint is decreased total and differential (lymphocytes, basophils, monocytes, and LUC) WBC count in female rats. Although the study is unpublished, it was performed according to GLP principles and otherwise meets the standards of study design and performance, with numbers of animals, examination of potential toxicity endpoints, and presentation of information. Details are provided in the "Review of Potentially Relevant Data" section. It is possible that peer-review of this unpublished study may upgrade the screening-level value to a provisional value.

Benchmark dose (BMD) analysis of total WBC count in female rats was conducted using appropriate continuous-variable models (polynomial, power, Hill, linear) in EPA's BMD software (Version 2.1.2) according to current EPA technical guidance. A benchmark response (BMR) of one standard deviation change from the control mean is selected in the absence of a biological rationale for using an alternative BMR. Results of the BMD analysis indicate poor global fit (goodness-of-fit $p < 0.10$) of all continuous models for nonconstant (modeled) variance

(see Table A.1). The high-dose group did not negatively impact low-dose fit. The homogeneity variance *p*-value of less than <0.1 indicates that nonconstant variance is the appropriate variance model (and therefore inappropriate to model constant variance for these data). Because all nonconstant variance models exhibited poor global fit to the data, a BMDL is not used as the POD.

Table A.1. Model Predictions for Total White Blood Cell Counts in Female Rats Exposed to Sulfolane in Drinking Water for 13 Weeks[a]

Model	Homogeneity Variance *p*-value	Goodness of Fit *p*-value[b]	AIC for Fitted Model	BMD_{1SD} (mg/kg-d)	$BMDL_{1SD}$ (mg/kg-d)	Conclusions
Hill (nonconstant variance)	0.036	0.027	112.41	9.26	-999.00	Invalid BMDL p-score 4 < 0.1
Linear (nonconstant variance)	0.036	0.008	115.30	190.43	131.06	Lowest AIC p-score 4 < 0.1
Polynomial (nonconstant variance)	0.036	0.008	115.30	190.43	131.06	Lowest AIC p-score 4 < 0.1 Maximum order beta = 0 β2 = 0 β3 = 0 β4 = 0
Power (nonconstant variance)	0.036	0.008	115.30	190.43	131.06	Lowest AIC p-score 4 < 0.1 hit bound (power = 1)

[a]Huntingdon Life Sciences (2001).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL lower confidence limit (95%) on the benchmark dose.

The NOAEL of 2.9 mg/kg-day is selected as the POD. No dosimetric adjustments are made because sulfolane was administered continuously via drinking water, and study authors calculated average daily dose based on body weight and drinking water consumption data in the principal study. No animal-to-human body weight adjustment is used for oral noncancer assessments.

The screening subchronic p-RfD for sulfolane, based on a NOAEL of 2.9 mg/kg-day in female rats, is derived as follows:

Screening Subchronic p-RfD = NOAEL ÷ UF
= 2.9 mg/kg-day ÷ 300
= **1×10^{-2} mg/kg-day**

Table A.2 summarizes the uncertainty factors for the screening chronic p-RfD of sulfolane.

Table A.2. Uncertainty Factors for Screening Subchronic p-RfD of Sulfolane

UF	Value	Justification	Notes
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans.	
UF_D	3	A UF_D of 3 is selected because there is an acceptable developmental study in mice (Zhu et al., 1987d), but a screening-level one-generation reproduction study in rats (Ministry of Health and Welfare Japan, 1999) via the oral route was deemed inadequate to reduce the uncertainty factor further.	The developmental study in mice was conducted soundly and identified teratogenic effects and is therefore considered a valid study.
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response to humans.	
UF_L	1	A UF_L of 1 is applied for using a POD based on a NOAEL.	
UF_S	1	A UF_S of 1 is applied because a subchronic study was utilized.	
UF_C ≤3000	300		

Derivation of Screening Chronic Provisional RfD (Chronic p-RfD)

The unpublished study by Huntingdon Life Sciences (2001) is selected as the principal study for derivation of the screening chronic p-RfD. For the same reasons listed above in the screening subchronic provisional RfD discussion, the study by Huntingdon Life Sciences (2001) meets standards of study design and performance. Details are provided in the "Review of Potentially Relevant Data" section. It is possible that peer-review of this unpublished study may upgrade the screening-level value to a provisional value.

The screening chronic p-RfD for sulfolane, based on a NOAEL of 2.9 mg/kg-day in female rats, is derived as follows:

Screening Chronic p-RfD = NOAEL ÷ UF
= 2.9 mg/kg-day ÷ 3000
= **1×10^{-3} mg/kg-day**

Table A.3 summarizes the uncertainty factors for the screening chronic p-RfD of sulfolane.

Table A.3. Uncertainty Factors for Screening Chronic p-RfD of Sulfolane

UF	Value	Justification	Notes
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans.	
UF_D	3	A UF_D of 3 is selected because there is an acceptable developmental study in mice (Zhu et al., 1987d) and a screening-level one-generation reproduction study in rats (Ministry of Health and Welfare Japan, 1999) via the oral route.	The developmental study in mice was conducted soundly and identified teratogenic effects and is therefore considered a valid study.
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response to humans.	
UF_L	1	A UF_L of 1 is applied for using a POD based on a NOAEL.	
UF_S	10	A UF_S of 10 is applied because a subchronic study is utilized.	
UF_C ≤3000	3000		

DERIVATION OF SCREENING PROVISIONAL INHALATION REFERENCE CONCENTRATION

Derivation of Screening Chronic Provisional RfC (Chronic p-RfC)

The POD in the Anderson 1977f study is an unadjusted NOAEL of 20 mg/m^3 as reported by the study authors. Dosimetric adjustments were performed for continuous duration. Conversion to HEC is not performed due to inadequate information on aerosol particle size (no information was given to determine the MMAD).

$NOAEL_{ADJ}$ = NOAEL × (Hours per Day Dosed ÷ 24) × (Days Dosed ÷ Total Study Days)
= 20 mg/m^3 × (23 ÷ 24) × (95 Days Dosed ÷ 95 Total Study Days)
= 20 × 0.958
= 19.2 mg/m^3

Screening Chronic p-RfC = $NOAEL_{ADJ} \div UF$
= $19.2\ mg/m^3 \div 10{,}000$
= $\mathbf{2 \times 10^{-3}\ mg/m^3}$

Table A.4 summarizes the uncertainty factors for the chronic p-RfC of sulfolane.

Table A.4. Uncertainty Factors for Chronic p-RfC of Sulfolane

UF	Value	Justification	Notes
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between dogs and humans.	Dosimetric conversion is not performed due to missing aerosol size information.
UF_D	10	A UF_D of 10 is selected because there are no acceptable two-generation reproduction studies or developmental studies via the inhalation route, and there is no indication of any other relevant studies that may be relevant for database uncertainty factor.	
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response to humans.	
UF_L	1	A UF_L of 1 is applied because a NOAEL was used.	
UF_S	10	A UF_S of 10 is applied because a subchronic study is utilized and extrapolated for a chronic exposure duration.	
UF_C ≤3000	10,000		

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APPENDIX B. DATA TABLES

Table B.1. Mean Body Weight and Survival of Male and Female CD Rats After Exposure to Sulfolane for 13 Weeks in Drinking Water[a]

		Exposure Group, mg/L (Average Daily Dose, mg/kg-d)[b]				
Male		**0**	**25 (2.1)**	**100 (8.8)**	**400 (35.0)**	**1600 (131.7)**
No. of animals		10	10	10	10	10
Body weight[c] (g)	Week 0	192 ± 9.6	196 ± 6.5 (102)	188 ± 9.5 (98)	190 ± 7.8 (99)	193 ± 12.8 (101)
	Week 1	251 ± 10.7	253 ± 8.7 (101)	247 ± 11.9 (98)	250 ± 11.9 (100)	243 ± 16.5 (97)
	Week 2	306 ± 13.2	313 ± 10.3 (102)	305 ± 11.8 (100)	310 ± 18.1 (101)	302 ± 20.8 (99)
	Week 3	348 ± 17.7	357 ± 10.1 (103)	348 ± 15.0 (100)	350 ± 23.3 (101)	347 ± 26.6 (100)
	Week 4	385 ± 18.7	395 ± 13.5 (103)	383 ± 19.2 (99)	388 ± 31.6 (101)	385 ± 29.5 (100)
	Week 5	418 ± 21.7	427 ± 11.1 (102)	412 ± 24.3 (99)	412 ± 32.2 (99)	416 ± 34.0 (100)
	Week 6	437 ± 23.1	453 ± 14.3 (104)	437 ± 29.0 (100)	435 ± 34.3 (100)	441 ± 36.7 (101)
	Week 7	457 ± 25.8	467 ± 14.6 (102)	457 ± 34.5 (100)	455 ± 35.0 (100)	464 ± 38.3 (102)
	Week 8	478 ± 26.1	490 ± 17.3 (103)	478 ± 34.1 (100)	475 ± 37.9 (99)	488 ± 39.2 (102)
	Week 9	498 ± 28.5	514 ± 16.9 (103)	497 ± 38.8 (100)	494 ± 42.2 (99)	509 ± 42.1 (102)
	Week 10	515 ± 30.4	529 ± 20.7 (103)	511 ± 45.9 (99)	511 ± 41.9 (99)	525 ± 43.7 (102)
	Week 11	524 ± 31.5	538 ± 22.8 (103)	522 ± 43.8 (100)	523 ± 45.8 (100)	541 ± 44.7 (103)
	Week 12	541 ± 34.9	558 ± 27.5 (103)	540 ± 49.6 (100)	541 ± 48.6 (100)	558 ± 47.9 (103)
	Week 13	538 ± 32.2	553 ± 26.4 (103)	539 ± 47.9 (100)	536 ± 48.7 (100)	556 ± 51.0 (103)
Body weight gain (g)	Week 0–13	346 ± 37.4	357 ± 26.1 (103)	351 ± 48.2 (101)	346 ± 43.7 (100)	363 ± 43.0 (105)
Survival[d]		10/10 (100)	10/10 (100)	10/10 (100)	10/10 (100)	10/10 (100)
Female		**0**	**25 (2.9)**	**100 (10.6)**	**400 (42.0)**	**1600 (191.1)**
No. of animals		10	10	10	10	10
Body weight (g)	Week 0	163 ± 10.8	160 ± 10.4 (98)	159 ± 7.5 (98)	160 ± 5.3 (98)	158 ± 11.2 (97)
	Week 1	187 ± 14.3	185 ± 14.2 (99)	185 ± 8.7 (99)	187 ± 6.7 (100)	178 ± 13.0 (95)
	Week 2	208 ± 14.4	210 ± 14.5 (101)	208 ± 9.5 (100)	210 ± 8.8 (101)	200 ± 16.5 (96)
	Week 3	226 ± 15.6	227 ± 15.5 (100)	222 ± 12.4 (98)	225 ± 10.1 (100)	216 ± 18.7 (96)
	Week 4	238 ± 16.1	245 ± 15.1 (103)	235 ± 14.6 (99)	237 ± 12.7 (100)	228 ± 18.0 (96)
	Week 5	248 ± 15.4	257 ± 20.1 (104)	248 ± 14.0 (100)	251 ± 12.5 (101)	237 ± 18.0 (96)
	Week 6	254 ± 17.6	266 ± 18.5 (105)	254 ± 15.0 (100)	261 ± 13.4 (103)	246 ± 20.5 (97)
	Week 7	262 ± 19.2	274 ± 18.3 (105)	259 ± 15.8 (99)	268 ± 15.6 (102)	250 ± 22.0 (95)
	Week 8	267 ± 18.5	281 ± 19.3 (105)	262 ± 17.8 (98)	271 ± 16.0 (101)	259 ± 19.4 (97)
	Week 9	272 ± 18.9	290 ± 22.6 (107)	275 ± 16.3 (101)	284 ± 17.5 (104)	265 ± 20.8 (97)

Table B.1. Mean Body Weight and Survival of Male and Female CD Rats After Exposure to Sulfolane for 13 Weeks in Drinking Water[a]

		Exposure Group, mg/L (Average Daily Dose, mg/kg-d)[b]				
	Week 10	279 ± 16.5	297 ± 24.3 (106)	278 ± 16.1 (100)	291 ± 17.6 (104)	272 ± 22.2 (97)
	Week 11	284 ± 18.0	300 ± 23.3 (106)	280 ± 18.0 (99)	292 ± 20.2 (103)	276 ± 23.3 (97)
	Week 12	287 ± 18.0	304 ± 22.3 (106)	282 ± 19.5 (98)	295 ± 18.1 (103)	279 ± 20.9 (97)
	Week 13	283 ± 19.8	303 ± 26.0 (107)	282 ± 17.1 (100)	292 ± 19.9 (103)	276 ± 22.2 (98)
Body weight gain (g)	Week 0–13	120 ± 12.1	143 ± 19.4[c] (119)	123 ± 12.4 (103)	132 ± 23.3 (110)	118 ± 16.3 (98)
Survival		10/10 (100)	10/10 (100)	10/10 (100)	10/10 (100)	10/10 (100)

[a]Huntingdon Life Sciences (2001).
[b]Average daily doses (mg/kg-day) were calculated by study authors.
[c]Weights expressed as mean ± SD (% of control).
[d]Survival expressed as number surviving/total number (% survival).
[e]Significantly different from control ($p < 0.05$); test was not reported.

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Table B.2. Mean Food Conversion Efficiency in Male and Female CD Rats After Exposure to Sulfolane for 13 Weeks in Drinking Water[a]

Parameter		Exposure Group, mg/L (Average Daily Dose, mg/kg-d)[b]				
Male		**0**	**25 (2.1)**	**100 (8.8)**	**400 (35.0)**	**1600 (131.7)**
No. of animals		10	10	10	10	10
Food efficiency[c]	Week 1	28.5	27.3	29.2	29.0	26.2
	Week 2	23.6	26.1	26.2	26.8	27.3
	Week 3	18.9	19.0	19.6	18.2	21.2
	Week 4	18.1	17.8	17.1	17.9	18.2
	Week 5	15.8	14..6	14.1	11.7	15.7
	Week 6	9.3	11.7	11.9	11.1	12.4
	Week 7	9.9	7.0	10.1	9.9	10.7
	Week 8	10.2	10.8	10.3	10.1	11.6
	Week 9	9.8	11.2	9.6	9.3	10.1
	Week 10	8.3	7.1	6.9	8.4	7.6
	Week 11	4.7	4.8	5.8	5.9	8.1
	Week 12	8.0	9.0	8.8	8.8	7.9
	Week 13	ND	ND	ND	ND	ND
Overall	Week 1–13	12.9	12.9	13.4	12.9	13.6
Female		**0**	**25 (2.9)**	**100 (10.6)**	**400 (42.0)**	**1600 (191.1)**
No. of animals		10	10	10	10	10
Food efficiency[c]	Week 1	16.8	17.7	18.9	19.6	14.8
	Week 2	14.8	17.0	16.7	16.3	16.0
	Week 3	12.5	11.6	10.3	10.5	11.1
	Week 4	9.0	12.3	8.7	8.7	8.2
	Week 5	6.9	7.7	8.8	9.6	6.5
	Week 6	3.9	6.6	4.4	6.8	6.6
	Week 7	5.0	5.2	3.2	5.4	3.3
	Week 8	4.0	4.9	2.4	2.1	5.6
	Week 9	4.4	5.9	9.7	8.9	4.7
	Week 10	4.9	5.1	1.9	4.9	4.9
	Week 11	3.9	1.9	1.4	0.7	1.9
	Week 12	2.6	3.4	1.3	2.1	2.2
	Week 13	ND	ND	0.2	ND	ND
Body weight gain (g)	Week 1–13	6.7	7.6	6.8	7.3	6.5

[a]Huntingdon Life Sciences (2001).
[b]Average daily doses (mg/kg-day) were calculated by study authors.
[c]Food conversion efficiency expressed as mean (%) and calculated as overall bodyweight gain divided by total food consumed.

ND = not determined; bodyweight loss or stasis.

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Table B.3. Selected Hematology Data for Rats Exposed Sulfolane for 13 Weeks in Drinking Water[a]

Parameter	Exposure Group, mg/L (Average Daily Dose, mg/kg-d)[b]				
Male	**0**	**25 (2.1)**	**100 (8.8)**	**400 (35.0)**	**1600 (131.7)**
No. of animals	9	10	10	9	9
MCV (fL)[c]	54.6 ± 0.89	53.8 ± 1.60 (99)	53.3 ± 1.41 (98)	54.4 ± 1.84 (100)	54.7 ± 1.58 (100)
WBC (× 10^9/L)	11.60 ± 2.719	11.61 ± 2.078 (100)	10.90 ± 1.534 (94)	9.47 ± 2.071 (82)	11.34 ± 2.074 (98)
Lymphocyte (× 10^9/L)	9.65 ± 2.430	9.77 ± 1.758 (101)	8.73 ± 1.267 (90)	7.90 ± 1.764 (82)	9.67 ± 1.919 (100)
Basophil (× 10^9/L)	0.02 ± 0.007	0.02 ± 0.009 (100)	0.02 ± 0.005 (100)	0.01 ± 0.007[e] (0.5)	0.01 ± 0.007[d] (0.5)
Monocyte (× 10^9/L)	0.36 ± 0.145	0.36 ± 0.104 (100)	0.38 ± 0.119 (106)	0.27 ± 0.134 (75)	0.25 ± 0.071 (69)
LUC (× 10^9/L)	0.22 ± 0.127	0.14 ± 0.042 (64)	0.16 ± 0.048 (73)	0.12 ± 0.050[e] (55)	0.14 ± 0.039[d] (64)
PT (sec)	13.4 ± 0.80	14.0 ± 1.32 (104)	13.3 ± 0.53 (99)	13.4 ± 1.27 (100)	14.3 ± 0.40[d] (107)
APTT (sec)	17.8 ± 2.24	18.2 ± 3.17 (102)	16.8 ± 2.34 (94)	17.8 ± 2.28 (100)	16.9 ± 2.25 (95)
Female	**0**	**25 (2.9)**	**100 (10.6)**	**400 (42.0)**	**1600 (191.1)**
No. of Animals	10	10	9	9	10
MCV (fL)	55.4 ± 1.39	55.1 ± 1.76 (99)	54.2 ± 1.19 (98)	55.2 ± 1.25 (100)	56.7 ± 1.39[d] (102)
WBC (× 10^9/L)	7.97 ± 2.213	7.63 ± 2.653 (96)	5.41 ± 1.392[e](69)	5.53 ± 1.756[e] (69)	4.54 ± 1.019[e] (57)
Lymphocyte (× 10^9/L)	6.98 ± 2.146	6.36 ± 2.452 (91)	4.39 ± 1.308[e] (63)	4.63 ± 1.564[e] (66)	3.73 ± 0.941[e] (53)
Basophil (× 10^9/L)	0.01 ± 0.006	0.01 ± 0.006 (100)	0.00 ± 0.005[d] (0)	0.00 ± 0.007[d] (0)	0.00 ± 0.004[e] (0)
Monocyte (× 10^9/L)	0.22 ± 0.080	0.23 ± 0.119 (105)	0.13 ± 0.053[d] (59)	0.13 ± 0.040[d] (59)	0.10 ± 0.040[e] (45)
LUC (× 10^9/L)	0.11 ± 0.040	0.11 ± 0.056 (100)	0.06 ± 0.023[d] (55)	0.06 ± 0.026[e] (55)	0.04 ± 0.019[e] (36)
PT (sec)	13.8 ± 0.97	14.1 ± 0.84 (102)	13.8 ± 0.85 (100)	14.1 ± 0.52 (102)	14.0 ± 0.94 (101)
APTT (sec)	17.4 ± 5.21	14.8 ± 1.65 (85)	15.4 ± 2.02 (89)	14.7 ± 1.33 (84)	14.2 ± 2.61[d] (82)

[a]Huntingdon Life Sciences (2001).
[b]Average daily doses (mg/kg-day) were calculated by study authors.
[c]Expressed as group mean ± SD (% of controls).
[d]Significantly different from control ($p \leq 0.05$); Williams' test or Shirley's test.
[e]Significantly different from control ($p \leq 0.01$); Williams' test.

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Table B.4. Selected Clinical Chemistry Data for Rats Exposed Sulfolane for 13 Weeks in Drinking Water[a]

Parameter	Exposure Group mg/L (Average Daily Dose, mg/kg-d)[b]				
Male	**0**	**25 (2.1)**	**100 (8.8)**	**400 (35.0)**	**1600 (131.7)**
No. of animals	10	10	10	10	10
ALT (U/L)[c]	49 ± 7.3	43 ± 9.1 (88)	45 ± 11.9 (92)	43 ± 9.5 (88)	38 ± 7.7[d] (78)
AST (U/L)	100 ± 55.1	77 ± 9.5 (77)	83 ± 21.1 (83)	82 ± 30.1 (82)	68 ± 10.0[e] (68)
Creatinine (µmol/L)	49 ± 3.5	48 ± 3.0 (98)	49 ± 2.9 (100)	51 ± 2.1 (104)	53 ± 1.8[e] (108)
Sodium (mmol/L)	141 ± 1.1	140 ± 1.3 (99)	141 ± 0.9 (100)	140 ± 0.9[d] (99)	138 ± 5.1[e] (98)
Total protein (g/L)	68 ± 2.3	69 ± 2.1 (101)	68 ± 2.5 (100)	67 ± 2.4 (99)	67 ± 2.2 (99)
Female	**0**	**25 (2.9)**	**100 (10.6)**	**400 (42.0)**	**1600 (191.1)**
No. of animals	10	10	10	10	10
ALT (U/L)	48 ± 37.5	54 ± 34.3 (113)	43 ± 10.9 (90)	43 ± 14.8 (90)	36 ± 6.1 (75)
AST (U/L)	81 ± 28.9	97 ± 61.2 (120)	85 ± 22.7 (105)	76 ± 18.4 (94)	72 ± 16.2 (89)
Creatinine (µmol/L)	52 ± 3.1	54 ± 5.5 (104)	56 ± 6.9 (108)	55 ± 6.2 (106)	53 ± 4.5 (102)
Sodium (mmol/L)	141 ± 1.0	140 ± 0.6[d] (99)	139 ± 0.9[e] (99)	140 ± 0.8[e] (99)	140 ± 0.8[e] (99)
Total protein (g/L)	75 ± 3.9	75 ± 2.8 (100)	75 ± 5.0 (100)	72 ± 2.6 (196)	73 ± 3.0 (97)

[a]Huntingdon Life Sciences (2001).
[b]Average daily doses (mg/kg-day) were calculated by study authors.
[c]Expressed as group mean ± SD (% of controls).
[d]Significantly different from control ($p \leq 0.05$); Williams' test or Shirley's test.
[e]Significantly different from control ($p \leq 0.01$); Williams' test or Shirley's test.

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Table B.5. Selected Histopathological Data in the Kidney for Rats Exposed Sulfolane for 13 Weeks in Drinking Water[a]

Parameter	Exposure Group mg/L (Average Daily Dose, mg/kg-d)[b]				
Male	**0**	**25 (2.1)**	**100 (8.8)**	**400 (35.0)**	**1600 (131.7)**
Cortical tubular basophilia[c]	3/10 (30)	4/10 (40)	3/10 (30)	3/10 (30)	7/10 (70)
Cortical tubules with hyaline droplets	4/10 (40)	2/10 (20)	4/10 (40)	9/10 (90)	9/10 (90)
Granular casts—medulla	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	2/10 (20)
Cortical scarring	1/10 (1)	0/10 (0)	0/10 (0)	1/10 (10)	1/10 (10)
Medullary cyst(s)	3/10 (30)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)
Interstitial nephritis	1/10 (10)	0/10 (0)	2/10 (20)	0/10 (0)	1/10 (10)
Mineralizations, corticomedullary	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)
Hyaline tubular casts	0/10 (0)	1/10 (10)	0/10 (0)	0/10 (0)	1/10 (10)
Hydronephrosis	0/10 (0)	0/10 (0)	0/10 (0)	1/10 (10)	2/10 (20)
Hyperplasia, papillary epithelium	0/10 (0)	0/10 (0)	0/10 (0)	1/10 (10)	1/10 (10)
Cortical cyst(s)	0/10 (0)	1/10 (10)	1/10 (10)	1/10 (10)	0/10 (0)
Papilla—dilated ducts	0/10 (0)	1/10 (10)	0/10 (0)	0/10 (0)	0/10 (0)
Female	**0**	**25 (2.9)**	**100 (10.6)**	**400 (42.0)**	**1600 (191.1)**
Cortical tubular basophilia	0/10 (0)	1/10 (10)	0/10 (0)	0/10 (0)	1/10 (10)
Cortical tubules with hyaline droplets	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)
Granular casts—medulla	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)
Cortical scarring	0/10 (0)	1/10 (10)	2/10 (20)	1/10 (10)	1/10 (10)
Medullary cyst(s)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)
Interstitial nephritis	0/10 (0)	0/10 (0)	0/10 (0)	1/10 (10)	1/10 (10)
Mineralizations, corticomedullary	1/10 (10)	0/10 (0)	1/10 (10)	0/10 (0)	3/10 (30)
Hyaline tubular casts	0/10 (0)	1/10 (10)	0/10 (0)	0/10 (0)	0/10 (0)
Hydronephrosis	0/10 (0)	0/10 (0)	0/10 (0)	1/10 (10)	0/10 (0)
Hyperplasia, papillary epithelium	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)
Cortical cyst(s)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)
Papilla—dilated ducts	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)

[a]Huntingdon Life Sciences (2001).
[b]Average daily doses (mg/kg-day) were calculated by study authors.
[c]Results presented no. of animals with lesion/no. of animals tested (% incidence).

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Table B.6. Mean Body Weight and Survival of Male and Female Sprague-Dawley Rats After Oral Exposure to Sulfolane for 28 Days[a]

		Exposure Group, mg/kg-d			
		0	60	200	700
Males—treatment period					
No. of animals		12	6	6	12
Body weight[b] (g)	Day 1	151 ± 3	151 ± 3 (100)	151 ± 4 (100)	151 ± 3 (100)
	Day 3	165 ± 4	165 ± 4 (100)	166 ± 6 (101)	146 ± 5[e] (88)
	Day 7	203 ± 7	200 ± 5 (99)	199 ± 5 (98)	177 ± 6[e] (87)
	Day 10	228 ± 10	225 ± 7 (99)	222 ± 5 (97)	198 ± 6[e] (87)
	Day 14	263 ± 13	260 ± 10 (99)	255 ± 6 (97)	226 ± 7[e] (86)
	Day 17	288 ± 17	284 ± 11 (99)	278 ± 8 (97)	247 ± 9[e] (86)
	Day 21	319 ± 21	312 ± 12 (98)	307 ± 8 (96)	276 ± 12[e] (87)
	Day 24	340 ± 23	330 ± 14 (97)	324 ± 10 (95)	292 ± 13[e] (86)
	Day 28	365 ± 27	351 ± 17 (96)	348 ± 7 (95)	317 ± 15[e] (87)
	Gain 1–28	214 ± 25	200 ± 16 (93)	197 ± 7 (92)	166 ± 15[e] (78)
Survival[c]		12/12 (100)	6/6 (100)	6/6 (100)	12/12 (100)
Males—recovery period					
Body weight[b] (g)	Day 28	371 ± 29	NE	NE	341 ± 15[e] (92)
	Day 31	390 ± 31	NE	NE	345 ± 15[e] (88)
	Day 35	413 ± 35	NE	NE	371 ± 17[d] (90)
	Day 28	430 ± 38	NE	NE	386 ± 19[d] (90)
	Day 42	446 ± 44	NE	NE	406 ± 22 (91)
	Gain 28–42	75 ± 15	NE	NE	92 ± 13 (123)
Survival[c]		12/12 (100)	NE	NE	12/12 (100)
Females—treatment period					
Body weight[b] (g)	Day 1	134 ± 4	134 ± 4 (100)	135 ± 5 (101)	134 ± 4 (100)
	Day 3	142 ± 5	143 ± 7 (101)	140 ± 7 (99)	127 ± 5[e] (89)
	Day 7	159 ± 6	160 ± 6 (101)	157 ± 7 (99)	146 ± 6[e] (92)
	Day 10	167 ± 8	169 ± 7 (101)	169 ± 9 (101)	157 ± 8[d] (94)
	Day 14	180 ± 11	180 ± 6 (100)	181 ± 11 (101)	169 ± 8[d] (94)
	Day 17	190 ± 12	190 ± 7 (100)	191 ± 13 (101)	178 ± 8 (94)
	Day 21	199 ± 13	200 ± 9 (101)	202 ± 14 (102)	189 ± 9 (95)
	Day 24	206 ± 15	203 ± 9 (99)	208 ± 15 (101)	195 ± 10 (95)
	Day 28	215 ± 16	213 ± 9 (99)	217 ± 18 (101)	205 ± 10 (95)

Table B.6. Mean Body Weight and Survival of Male and Female Sprague-Dawley Rats After Oral Exposure to Sulfolane for 28 Days[a]

		Exposure Group, mg/kg-d			
	Gain 1–28	81 ± 14	79 ± 6 (98)	82 ± 15 (101)	72 ± 10 (89)
Survival[c]		12/12 (100)	6/6 (100)	6/6 (100)	12/12 (100)
Females—recovery period					
Body weight[b] (g)	Day 28	214 ± 23	NE	NE	207 ± 13 (97)
	Day 31	219 ± 25	NE	NE	222 ± 14 (101)
	Day 35	226 ± 26	NE	NE	233 ± 17 (103)
	Day 28	233 ± 32	NE	NE	239 ± 20 (103)
	Day 42	239 ± 34	NE	NE	246 ± 22 (103)
	Gain 28–42	25 ± 12	NE	NE	40 ± 11 (160)
Survival[c]		12/12 (100)	NE	NE	12/12 (100)

[a]Ministry of Health and Welfare Japan (1996a).
[b]Weights expressed as mean ± SD (% of control).
[c]Survival expressed as number surviving/total number (% survival).
[d]Significantly different from control ($p = 0.05$); test was not reported.
[e]Significantly different from control ($p = 0.01$); test was not reported.

NE = not examined.

1

Table B.7. Mean Food Consumption Data of Male and Female Sprague-Dawley Rats After Oral Exposure to Sulfolane for 28 Days[a]

		Exposure Group (mg/kg-d)			
		0	60	200	700
Males—treatment period					
No. of cages		12	6	6	12
Food consumption[b] (g)	Week 1	25 ± 1	25 ± 3 (100)	25 ± 2 (100)	18 ± 3[c] (72)
	Week 2	29 ± 3	29 ± 3 (100)	29 ± 2 (100)	24 ± 2[c] (83)
	Week 3	30 ± 2	30 ± 2 (100)	31 ± 1 (103)	27 ± 2[c] (90)
	Week 4	32 ± 4	32 ± 2 (100)	33 ± 2 (103)	30 ± 3 (94)
Males—recovery period					
No. of cages		6	0	0	6
Food consumption (g)	Week 0	33 ± 5	NE	NE	30 ± 3 (91)
	Week 1	34 ± 4	NE	NE	34 ± 2 (100)
	Week 2	35 ± 5	NE	NE	35 ± 2 (100)
Females—treatment period					
No. of cages		12	6	6	12
Food consumption (g)	Week 1	19 ± 1	19 ± 1 (100)	19 ± 2 (100)	12 ± 3[c] (63)
	Week 2	19 ± 2	20 ± 1 (105)	20 ± 2 (105)	19 ± 1 (100)
	Week 3	21 ± 2	21 ± 2 (100)	22 ± 3 (105)	20 ± 1 (95)
	Week 4	21 ± 2	19 ± 2 (90)	21 ±3 (100)	21 ± 2 (100)
Females—recovery period					
No. of cages		6	0	0	6
Food consumption (g)	Week 0	21 ± 2	NE	NE	21 ± 2 (100)
	Week 1	21 ± 2	NE	NE	26 ± 1[c] (124)
	Week 2	22 ± 4	NE	NE	23 ± 3 (105)

[a]Ministry of Health and Welfare Japan (1996a)
[b]Food consumption expressed as mean ± SD (% of control).
[c]Significantly different from control ($p = 0.01$); test was not reported.

ND = not determined.

2

3

1

Table B.8. Incidences of Clinical Signs in Female Sprague-Dawley Rats After Oral Exposure to Sulfolane for 28 Days[a]

Weight	Exposure Group (mg/kg-d)			
	0	60	200	700
Treatment period				
No. of animals	12	6	6	12
Decreased locomotor activity[b]	0	0	0	3
Recovery period				
No. of animals	6	0	0	6
Decreased locomotor activity	0	NE	NE	0

[a]Ministry of Health and Welfare Japan (1996a).
[b]Parameter expressed as number of animals affected.

NE = not examined.

2
3

1

Table B.9. Selected Hematological Parameters of Male and Female Sprague-Dawley Rats After Oral Exposure to Sulfolane for 28 Days[a]

Parameter	Exposure Group (mg/kg-d)			
	0	60	200	700
Males—after treatment				
No. of animals	12	6	6	12
RBC (10^4/μL)[b]	765 ± 32	763 ± 43 (100)	763 ± 29 (100)	772 ± 22 (101)
MCV (fL)	59 ± 3	60 ± 3 (102)	59 ± 2 (100)	61 ± 2 (103)
MCHC (%)	34.6 ± 0.8	33.8 ± 0.4[c] (98)	33.5 ± 0.2[d] (97)	33.6 ± 0.4[d] (97)
WBC (10^2/μL)	60 ± 16	58 ± 19 (97)	58 ± 13 (97)	64 ± 7 (107)
Males—after recovery period				
No. of animals	6	0	0	6
RBC (10^4/μL)	784 ± 58	NE	NE	800 ± 49 (102)
MCV (fL)	58 ± 2	NE	NE	58 ± 2 (100)
MCHC (%)	34.3 ± 0.5	NE	NE	34.5 ± 0.8 (101)
WBC(10^2/μL)	76 ± 19	NE	NE	104 ± 22[c] (137)
Females—after treatment				
No. of animals	12	6	6	12
RBC (10^4/μL)	773 ± 21	778 ± 32 (101)	752 ± 23 (97)	778 ± 42 (101)
MCV (fL)	57 ± 2	57 ± 2 (100)	57 ± 1 (100)	58 ± 1 (102)
MCHC (%)	34.4 ± 0.4	34.9 ± 0.4 (101)	34.4 ± 0.7 (100)	33.9 ± 0.6 (99)
WBC (10^2/μL)	49 ± 12	41 ± 12 (84)	38 ± 12 (78)	36 ± 15 (73)
Females—after recovery period				
No. of animals	6	0	0	6
RBC (10^4/μL)	817 ± 16	NE	NE	781 ± 21[d] (96)
MCV (fL)	55 ± 1	NE	NE	57 ± 1[d] (104)
MCHC (%)	34.6 ± 0.7	NE	NE	34.5 ± 0.3 (100)
WBC(10^2/μL)	49 ± 14	NE	NE	69 ± 22 (141)

[a]Ministry of Health and Welfare Japan (1996a).
[b]Parameters expressed as mean ± SD (% of control).
[c]Significantly different from control ($p = 0.05$); test was not reported.
[d]Significantly different from control ($p = 0.01$); test was not reported.

RBC = red blood cells; MCV = mean corpuscular volume; MCHC = mean cell hemoglobin concentration; WBC = white blood cells; NE = not examined.

2

Table B.10. Selected Clinical Chemistry Parameters of Male and Female Sprague-Dawley Rats After Oral Exposure to Sulfolane for 28 Days[a]

Parameter	Exposure Group (mg/kg-d)			
	0	60	200	700
Males—after treatment				
No. of animals	6	6	6	6
Alanine aminotransferase (ALT; IU/L)[b]	28 ± 5	28 ± 6 (100)	27 ± 3 (96)	33 ± 5[c] (118)
Total protein (g/dL)	6.33 ± 0.22	6.12 ± 0.12 (97)	6.07 ± 0.13[c] (96)	6.35 ± 0.13 (100)
Thromboglobulin (mg/dL)	80 ± 25	71 ± 13 (89)	86 ± 17 (108)	110 ± 32 (138)
Glucose (mg/dL)	134 ± 11	142 ± 24 (106)	138 ± 9 (103)	130 ± 18 (97)
Total bilirubin (mg/dL)	0.35 ± 0.05	0.35 ± 0.05 (100)	0.40 ± 0.05 (114)	0.45 ± 0.03[d] (129)
ChE (IU/L)	25 ± 9	20 ± 6 (80)	26 ± 4 (104)	40 ± 12[c] (160)
Cl (mEq/L)	104 ± 0	104 ± 1 (100)	104 ± 1 (100)	102 ± 1[d] (98)
Creatinine (mg/dL)	0.51 ± 0.07	0.47 ± 0.06 (92)	0.50 ± 0.05 (98)	0.49 ± 0.04 (96)
Males—after recovery period				
No. of animals	6	0	0	6
Alanine aminotransferase (ALT; IU/L)	31 ± 6	NE	NE	36 ± 9 (116)
Total protein (g/dL)	6.29 ± 0.34	NE	NE	6.09 ± 0.14 (97)
Thromboglobulin (mg/dL)	90 ± 32	NE	NE	63 ± 16 (70)
Glucose (mg/dL)	157 ± 12	NE	NE	143 ± 8[c] (91)
Total bilirubin (mg/dL)	0.28 ± 0.02	NE	NE	0.30 ± 0.05 (107)
ChE (IU/L)	51 ± 22	NE	NE	45 ± 23 (88)
Cl (mEq/L)	103 ± 2	NE	NE	103 ± 1 (100)
Creatinine (mg/dL)	0.63 ± 0.03	NE	NE	0.57 ± 0.04[c] (90)
Females—after treatment				
No. of animals	6	6	6	6
Alanine aminotransferase (ALT; IU/L)	24 ± 5	24 ± 4 (100)	23 ± 4 (96)	35 ± 6[d] (146)
Total protein (g/dL)	6.26 ± 0.36	6.49 ± 0.26 (104)	6.41 ± 0.16 (102)	6.36 ± 0.15 (102)
Thromboglobulin (mg/dL)	26 ± 4	38 ± 12 (146)	44 ± 12[d] (169)	32 ± 12 (123)
Glucose (mg/dL)	130 ± 15	117 ± 13 (90)	124 ± 10 (95)	110 ± 4[c] (85)
Total bilirubin (mg/dL)	0.21 ± 0.01	0.22 ± 0.02 (105)	0.22 ± 0.2 (105)	0.24 ± 0.03 (114)
ChE (IU/L)	304 ± 175	296 ± 106 (97)	281 ± 60 (92)	294 ± 41 (97)
Cl (mEq/L)	106 ± 1	106 ± 1 (100)	106 ± 2 (100)	106 ± 1 (100)
Creatinine (mg/dL)	0.54 ± 0.05	0.55 ± 0.04 (102)	0.53 ± 0.02 (98)	0.53 ± 0.04 (98)

Table B.10. Selected Clinical Chemistry Parameters of Male and Female Sprague-Dawley Rats After Oral Exposure to Sulfolane for 28 Days[a]

Parameter	Exposure Group (mg/kg-d)			
	0	60	200	700
Females—after recovery period				
No. of animals	6	0	0	6
Alanine aminotransferase (ALT; IU/L)	27 ± 6	NE	NE	29 ± 6 (107)
Total protein (g/dL)	6.60 ± 0.29	NE	NE	6.62 ± 0.12 (100)
Thromboglobulin (mg/dL)	46 ± 15	NE	NE	61 ± 19 (133)
Glucose (mg/dL)	139 ± 13	NE	NE	125 ± 10 (90)
Total bilirubin (mg/dL)	0.29 ± 0.05	NE	NE	0.28 ± 0.02 (97)
ChE (IU/L)	292 ± 89	NE	NE	263 ± 47 (90)
Cl (mEq/L)	105 ± 2	NE	NE	105 ± 1 (100)
Creatinine (mg/dL)	0.65 ± 0.10	NE	NE	0.61 ± 0.05 (94)

[a]Ministry of Health and Welfare Japan (1996a)
[b]Parameters expressed as mean ± SD (% of control).
[c]Significantly different from control ($p = 0.05$); test was not reported.
[d]Significantly different from control ($p = 0.01$); test was not reported.

1
2

Table B.11. Selected Organ Weights of Male and Female Rats After Oral Exposure to Sulfolane for 28 Days[a]

Parameter		Exposure Group (mg/kg-d)			
		0	60	200	700
Males					
After treatment					
No. of animals		6	6	6	6
Weight[b]	Abs. spleen	0.68 ± 0.05	0.62 ± 0.07 (91)	0.62 ± 0.02 (91)	0.58 ± 0.10 (85)
	Rel. spleen	0.21 ± 0.02	0.20 ± 0.02 (95)	0.20 ± 0.01 (95)	0.20 ± 0.03 (95)
	Abs. liver	9.77 ± 0.72	9.70 ± 0.88 (99)	9.76 ± 0.37 (100)	9.23 ± 0.65 (94)
	Rel. liver	3.04 ± 0.22	3.05 ± 0.15 (100)	3.11 ± 0.10 (102)	3.22 ± 0.15 (106)
	Abs. brain	1.99 ± 0.10	2.03 ± 0.07 (102)	2.00 ± 0.08 (101)	1.95 ± 0.04 (98)
	Rel. brain	0.62 ± 0.03	0.64 ± 0.03 (103)	0.64 ± 0.03 (103)	0.68 ± 0.05[c] (110)
	Abs. kidney	2.47 ± 0.22	2.53 ± 0.14 (102)	2.48 ± 0.11 (100)	2.70 ± 0.30 (109)
	Rel. kidney	0.77 ± 0.04	0.80 ± 0.05 (104)	0.79 ± 0.05 (103)	0.94 ± 0.06[d] (122)
	Abs. heart	1.10 ± 0.11	1.11 ± 0.13 (101)	1.09 ± 0.05 (99)	1.10 ± 0.09 (100)
	Rel. heart	0.34 ± 0.03	0.35 ± 0.03 (103)	0.35 ± 0.01 (103)	0.39 ± 0.03[d] (115)
After recovery period					
No. of animals		6	0	0	6
Weight	Absolute spleen	0.77 ± 0.15	NE	NE	0.68 ± 0.09 (88)
	Relative spleen	0.19 ± 0.03	NE	NE	0.18 ± 0.02 (95)
	Abs. liver	11.98 ± 1.62	NE	NE	10.56 ± 0.49 (88)
	Rel. liver	2.96 ± 0.23	NE	NE	2.86 ± 0.11 (97)
	Abs. brain	2.08 ± 0.09	NE	NE	2.00 ± 0.06 (96)
	Rel. brain	0.52 ± 0.04	NE	NE	0.54 ± 0.04 (104)
	Abs. kidney	2.69 ± 0.21	NE	NE	2.60 ± 0.27 (97)
	Rel. kidney	0.67 ± 0.05	NE	NE	0.71 ± 0.08 (106)
	Abs. heart	1.28 ± 0.12	NE	NE	1.25 ± 0.11 (98)
	Rel. heart	0.32 ± 0.02	NE	NE	0.34 ± 0.03 (106)
Females					
After treatment					
Sample size		6	6	6	6
Weight	Absolute spleen	0.48 ± 0.06	0.43 ± 0.05 (90)	0.44 ± 0.08 (92)	0.37 ± 0.03[c] (77)

Table B.11. Selected Organ Weights of Male and Female Rats After Oral Exposure to Sulfolane for 28 Days[a]

Parameter		Exposure Group (mg/kg-d)			
	Relative spleen	0.24 ± 0.03	0.22 ± 0.03 (92)	0.23 ± 0.05 (96)	0.20 ± 0.01 (83)
	Abs. liver	5.95 ± 0.32	5.81 ± 0.31 (98)	6.29 ± 0.96 (106)	5.64 ± 0.38 (95)
	Rel. liver	3.00 ± 0.18	2.97 ± 0.08 (99)	3.19 ± 0.27 (106)	3.01 ± 0.15 (100)
	Abs. brain	1.82 ± 0.05	1.87 ± 0.04 (103)	1.83 ± 0.03 (101)	1.81 ± 0.05 (99)
	Rel. brain	0.92 ± 0.05	0.96 ± 0.06 (104)	0.94 ± 0.07 (102)	0.97 ± 0.05 (105)
	Abs. kidney	1.61 ± 0.11	1.58 ± 0.12 (98)	1.63 ± 0.12 (101)	1.60 ± 0.13 (99)
	Rel. kidney	0.82 ± 0.07	0.81 ± 0.07 (99)	0.83 ± 0.03 (101)	0.85 ± 0.07 (104)
	Abs. heart	0.77 ± 0.03	0.74 ± 0.04 (96)	0.76 ± 0.07 (99)	0.73 ± 0.06 (95)
	Rel. heart	0.39 ± 0.02	0.38 ± 0.03 (97)	0.39 ± 0.02 (100)	0.39 ± 0.02 (100)
After recovery period					
Sample size		6	0	0	6
Weight	Absolute spleen	0.44 ± 0.06	NE	NE	0.53 ± 0.05[c] (120)
	Relative spleen	0.20 ± 0.02	NE	NE	0.24 ± 0.02[c] (120)
	Abs. liver	6.00 ± 0.84	NE	NE	6.69 ± 0.60 (112)
	Rel. liver	2.74 ± 0.15	NE	NE	2.98 ± 0.09[d] (109)
	Abs. brain	1.84 ± 0.09	NE	NE	1.85 ± 0.05 (101)
	Rel. brain	0.85 ± 0.08	NE	NE	0.83 ± 0.06 (98)
	Abs. kidney	1.58 ± 0.23	NE	NE	1.58 ± 0.08 (100)
	Rel. kidney	0.72 ± 0.05	NE	NE	0.71 ± 0.04 (99)
	Abs. heart	0.79 ± 0.09	NE	NE	0.84 ± 0.06 (106)
	Rel. heart	0.36 ± 0.02	NE	NE	0.38 ± 0.03 (106)

[a]Ministry of Health and Welfare Japan (1996a).
[b]Absolute weights expressed as mean ± SD (% of control); Relative weights expressed as percentage of body weight.
[c]Significantly different from control ($p = 0.05$); test was not reported.
[d]Significantly different from control ($p = 0.01$); test was not reported.

NE = not examined.

Table B.12. Incidence of Selected Histopathological Findings in the Kidneys of Male and Female Sprague-Dawley Rats After Oral Exposure to Sulfolane for 28 Days[a]

Parameter		Exposure Group (mg/kg-d)			
		0	60	200	700
Males—after treatment					
No. of animals		6	6	6	6
	Grade[b]				
Hyaline droplets in prox. tubule epithelium	+	1	0	5	1
	++	0	0	1	4
	+++	0	0	0	1
Total incidence		1	0	6[d]	6[d]
Eosinophilic bodies in proximal tubule	+	0	0	5[d]	4[c]
Tubular basophilic change	+	2	1	2	5
Focul tubular dilatation with or without hyaline casts	+	1	1	0	0
Distal tubular dilatation	+	0	0	1	1
Males—after recovery period					
No. of animals		6	0	0	6
Hyaline droplets in prox. tubule epithelium	+	1	NE	NE	3
	++	0	NE	NE	0
	+++	0	NE	NE	0
Total incidence		1	NE	NE	3
Eosinophilic bodies in proximal tubule	+	1	NE	NE	0
Tubular basophilic change	+	4	NE	NE	5
Focul tubular dilatation with or without hyaline casts	+	0	NE	NE	0
Distal tubular dilatation	+	0	NE	NE	0
		0	**60**	**200**	**700**
Females—after treatment					
No. of animals		6	6	6	6
	Grade				
Tubular basophilic change	+	2	NE	NE	1
Fibrotic focus	+	0	NE	NE	1

Table B.12. Incidence of Selected Histopathological Findings in the Kidneys of Male and Female Sprague-Dawley Rats After Oral Exposure to Sulfolane for 28 Days[a]

Parameter		Exposure Group (mg/kg-d)			
		0	60	200	700
Females—after recovery					
No. of animals	+	6	NE	NE	6
Tubular basophilic change	+	NE	NE	NE	NE
Fibrotic focus	+	NE	NE	NE	NE

[a]Ministry of Health and Welfare Japan (1996a).
[b]Severity grades: + = slight, ++ = moderate, +++ = marked
[c]Significantly different from control ($p = 0.05$); test was not reported.
[d]Significantly different from control ($p = 0.01$); test was not reported.

NE = not examined.

Table B.13. Clinical Chemistry and Pathology Data of Guinea Pigs Orally Exposed to Sulfolane for 3 or 6 months[a]

Parameter	Exposure Group (mg/kg-d)				
	0	0.25	2.5	25	250
At 3 months					
ALT (IU/100mL)[b]	59.4	DNP	DNP	40.8	45.8
AST (IU/100mL)	106	DNP	DNP	DNP	71
Marrow cell count ($\times 10^4/mm^3$)	16.43	DNP	10.99	12.25	10.56
Spleen—dispersion of white pulp	0/14	0/14	1/14	2/14	6/14
At 6 months					
Spleen—dispersion of white pulp	0/25	0/22	2/26	2/25	7/22
Liver—fatty degeneration	0/25	0/22	2/26	4/25	7/22

[a]Zhu et al. (1987c).
[b]Data are assumed to be group mean. No standard deviation or standard error was provided.
[c]Data are provided as incidence (No. of animals with effect/No. of animals in test group).

DNP = data not provided.

1

Table B.14. Mean Body Weight and Survival of Male and Female Rats After Oral Exposure to Sulfolane for 41–50 Days[a]

Parameter		Exposure Group (mg/kg-d)			
Male		**0**	**60**	**200**	**700**
Sample size		12	12	12	12 (Days 1–4; 11 thereafter)
Weight[b] (g)	Day 1	367.2 ± 6.7	366.6 ± 5.8 (100)	367.1 ± 6.2 (100)	366.8 ± 5.5 (100)
	Day 4	382.0 ± 10.5	379.7 ± 7.0 (99)	372.3 ± 8.9[d] (97)	322.5 ± 9.8[c] (84)
	Day 8	393.5 ± 11.7	391.8 ± 8.4 (100)	386.5 ± 10.1 (98)	322.0 ± 18.6[c] (82)
	Day 11	403.5 ± 14.1	403.0 ± 13.0 (100)	399.6 ± 13.1 (99)	341.6 ± 14.6[c] (85)
	Day 15	419.3 ± 15.7	416.8 ± 16.6 (99)	417.5 ± 14.1 (100)	370.5 ± 14.1[c] (88)
	Day 18	428.3 ± 16.9	427.3 ± 16.4 (100)	420.5 ± 11.5 (98)	373.1 ± 14.6[c] (87)
	Day 22	445.9 ± 15.4	442.4 ± 16.1 (99)	439.0 ± 12.9 (98)	399.7 ± 18.2[c] (90)
	Day 25	452.3 ± 18.2	453.2 ± 17.7 (100)	450.2 ± 13.6 (100)	411.7 ± 21.8[c] (91)
	Day 29	469.9 ± 19.7	473.3 ± 23.7 (101)	467.5 ± 13.6 (99)	426.8 ± 20.6[c] (91)
	Day 32	474.5 ± 21.0	474.5 ± 22.2 (100)	473.2 ±15.1 (100)	432.9 ± 21.1[c] (91)
	Day 36	479.8 ± 23.3	479.0 ± 20.6 (100)	479.6 ± 15.4 (100)	436.4 ± 20.4[c] (91)
	Day 39	486.4 ± 23.7	485.7 ± 24.9 (100)	485.9 ± 14.3 (100)	440.1 ± 20.1[c] (90)
	Day 43	493.1 ± 25.6	492.2 ± 26.7 (100)	494.2 ± 12.1 (100)	442.8 ± 19.7[c] (90)
	Day 46	495.9 ± 24.2	496.5 ± 27.1 (100)	496.7 ±13.9 (100)	448.2 ± 17.8[c] (90)
	Day 49	500.9 ± 25.6	503.3 ± 25.8 (100)	501.7 ± 13.2 (100)	449.4 ± 21.9[c] (90)
Survival[c]		12/12	12/12	12/12	11/12
Female		**0**	**60**	**200**	**700**
Sample size (except where indicated)		12	12	12	12
Weight (g)	Day 1	218.3 ± 6.5	218.3 ± 6.1 (100)	218.8 ± 6.0 (100)	218.6 ± 5.8 (100)
	Day 4	218.4 ± 6.5	216.1 ± 7.9 (99)	213.3 ± 6.8 (98)	195.1 ± 6.6[c] (89)
	Day 8	224.2 ± 9.0	219.8 ± 7.1 (98)	217.9 ± 7.4 (97)	201.3 ± 6.8[c] (90)
	Day 11	229.4 ± 6.5	225.1 ± 8.6 (98)	222.8 ± 7.9 (97)	216.3 ± 9.1[c] (94)
	Day 15	234.3 ± 7.9	231.0 ± 10.9 (99)	230.7 ± 8.7 (98)	226.7 ± 11.2 (97)
	Day 18	250.0 (n = 2)	253.5 (n = 2) (101)	243.3 ± 11.7 (n = 4) (97)	258.0 (n =5) (103)
	Day 22	NR	NR	NR	258.0 (n = 2)
	Day 25	NR	NR	NR	272.5 (n = 2)
	Day 29	NR	NR	NR	270.0 (n = 1)

Table B.14. Mean Body Weight and Survival of Male and Female Rats After Oral Exposure to Sulfolane for 41–50 Days[a]

Parameter		Exposure Group (mg/kg-d)			
Pregnancy and Lactation Weights					
Sample size		11	12	10	10
Pregnancy Day 0		240.4 ± 9.9	236.8 ± 11.9 (99)	236.9 ± 8.9 (99)	235.5 ± 23.1 (98)
	Day 7	272.8 ± 8.1	269.2 ± 14.0 (99)	267.8 ± 9.7 (98)	262.8 ± 16.0 (96)
	Day 14	305.9 ± 11.6	300.3 ± 16.1 (98)	295.0 ± 12.2 (96)	291.9 ± 15.1 (95)
	Day 21	388.8 ± 18.0	383.1 ± 22.1 (99)	375.5 ± 14.4 (97)	369.1 ± 29.8 (95)
Lactation Day 0		274.1 ± 14.3	269.9 ± 17.7 (98)	265.0 ± 9.2 (97)	269.4 ± 8.9 (98)
	Day 4	292.9 ± 17.2	290.3 ± 19.2 (99)	284.3 ± 16.5 (97)	272.2 ± 12.7 (n = 5) (93)
Survival		12/12	12/12	12/12	11/12

[a]Ministry of Health and Welfare Japan (1999).
[b]Weights expressed as mean ± SD (% of control).
[c]Survival expressed as number surviving/total number (% survival); % is calculated.
[d]Significantly different from control ($p < 0.05$); test was not reported.
[e]Significantly different from control ($p < 0.01$); test was not reported.

NR = Not reported.

Table B.15. Food Consumption of Male and Female Rats During Oral Exposure to Sulfolane for 41–50 Days[a]

Parameter		Exposure Group (mg/kg-d)			
Male		**0**	**60**	**200**	**700**
No. of animals		12	12	12	12 (Days 1–4; 11 thereafter)
Consumption[b] (g/day)	Day 3	26.9 ± 1.9	27.1 ± 1.3 (101)	24.0 ± 2.3[d] (89)	13.1 ± 2.8[d] (49)
	Day 6	27.6 ± 1.8	28.9 ± 1.7 (105)	26.9 ± 1.4 (97)	12.4 ± 4.9[d] (45)
	Day 10	27.6 ± 2.2	28.9 ± 2.3 (105)	28.1 ± 2.0 (102)	28.1 ± 2.2 (102)
	Day 13	27.7 ± 1.6	28.1 ± 1.4 (101)	28.0 ± 2.0 (101)	27.2 ± 1.9 (98)
	Day 31	25.2 ± 1.6	25.7 ± 1.8 (102)	26.1 ± 1.4 (104)	26.3 ± 2.5 (104)
	Day 34	25.5 ± 1.5	26.7 ± 2.7 (105)	26.8 ± 1.8 (105)	26.4 ± 2.2 (104)
	Day 38	25.3 ± 1.1	26.2 ± 2.4 (104)	25.5 ± 2.0 (101)	26.0 ± 1.8 (103)
	Day 41	25.5 ± 1.2	26.7 ± 3.5 (105)	25.6 ± 2.0 (100)	24.9 ± 2.1 (98)
	Day 45	25.3 ± 3.2	27.6 ± 3.1 (109)	25.3 ± 2.2 (100)	24.8 ± 2.4 (98)
	Day 48	24.5 ± 1.6	27.4 ± 3.1[c] (112)	23.6 ± 2.1 (96)	24.0 ± 3.1 (98)
Female		**0**	**60**	**200**	**700**
No. of animals (except where indicated)		12	12	12	12
Consumption[b] (g/day)	Day 3	16.3 ± 1.7	15.0 ± 2.0 (92)	14.7 ± 1.7 (90)	9.1 ± 1.1[d] (56)
	Day 6	18.0 ± 1.4	17.5 ± 2.2 (97)	17.4 ± 2.0 (97)	10.4 ± 2.4[d] (58)
	Day 10	18.8 ± 1.4	18.7 ± 2.2 (99)	19.0 ± 2.6 (101)	20.7 ± 1.7 (110)
	Day 13	17.9 ± 2.3	17.8 ± 2.3 (99)	18.6 ± 2.1 (104)	19.5 ± 3.3 (109)
Pregnancy and Lactation					
No. of animals		11	12	10	10
Pregnancy Day 2		21.0 ± 1.7	20.9 ± 3.1 (100)	21.0 ± 2.1 (100)	18.7 ± 2.2 (89)
	Day 9	23.0 ± 1.8	22.9 ± 1.8 (100)	22.9 ± 2.0 (100)	21.2 ± 1.1 (92)
	Day 16	22.5 ± 0.9	22.3 ± 2.3 (99)	21.4 ± 1.7 (95)	22.6 ± 2.2 (100)
	Day 21	20.2 ± 2.6	19.4 ± 2.2 (96)	20.3 ± 1.4 (100)	21.5 ± 2.7 (106)
Lactation Day 4		30.3 ± 5.1	30.2 ± 4.1 (100)	29.8 ± 4.9 (98)	18.4 ± 9.8[d] (61)

[a]Ministry of Health and Welfare Japan (1999).
[b]Consumption expressed as mean g/day ± SD (% of control).
[c]Significantly different from control ($p < 0.05$); test was not reported.
[d]Significantly different from control ($p < 0.01$); test was not reported.

NR = Not reported.

Table B.16. Ovary Weight of Female Rats After Oral Exposure to Sulfolane for 41–50 Days[a]

Weight	Exposure Group (mg/kg-d)			
	0	60	200	700
Sample size	12	12	12	12
Final Body Weight[b] (g)	289.0 ± 21.3	290.3 ± 19.2 (100)	284.0 ± 15.0 (98)	268.3 ± 14.2[c] (93)
Ovaries (mg)	94.79 ± 11.71	95.51 ± 11.57 (101)	98.39 ± 10.42 (104)	108.63 ± 17.99 (115)
(mg %)	32.90 ± 4.36	33.04 ± 4.62 (100)	34.66 ± 3.33 (105)	40.45 ± 5.92[d] (123)

[a]Ministry of Health and Welfare Japan (1999).
[b]Weights expressed as mean ± SD (% of control).
[c]Significantly different from control ($p < 0.05$); test was not reported.
[d]Significantly different from control ($p < 0.01$); test was not reported.

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Table B.17. Selected Reproductive Parameters of Female Rats After Oral Exposure to Sulfolane for 41–50 Days[a]

Parameter	Exposure Group (mg/kg-d)			
	0	60	200	700
Number of females	12	12	12	12
Number of estrous cases before mating (14 d)[b]	3.5 ± 0.5	3.3 ± 0.5 (94)	3.2 ± 0.4 (91)	2.2 ± 0.9[e] (63)
Number of pregnant females	11	12	10	10
Fertility index[c]	91.7	100.0	83.3	90.9
Number of pregnant females with live pups	11	12	10	10
Number of males	12	12	12	11
Number of males with successful copulation	12	12	12	10
Copulation index[d]	100.0	100.0	100.0	91.7

[a]Ministry of Health and Welfare Japan (1999).
[b]Presented as mean ± SD (% of control)
[c]Express as %; calculated using the equation: (number of females with successful copulation/number if females) × 100.
[d]Expressed as %; calculated using the equation: (number of males with successful copulation/number of males) × 100.
[e]Significantly different from control ($p < 0.01$); test was not reported.

2
3

Table B.18. Selected Pup Observations of Female Rats Exposed to Sulfolane for 41–50 Days[a]

Parameter	Exposure Group (mg/kg-d)			
	0	60	200	700
Number of dams	11	12	10	10
Birth index[b]	96.3 ± 6.5	95.8 ± 4.8 (99)	90.5 ± 5.1[f] (94)	71.6 ± 26.2[g] (74)
Dead pups on Lactation Day 0	0.3 ± 0.5	0.2 ± 0.4 (67)	0.2 ± 0.4 (67)	3.6 ± 4.4[g] (1200)
Delivery index[c]	98.1 ± 4.5	96.9 ± 4.0 (99)	91.8 ± 4.1[f] (94)	94.0 ± 6.7 (96)
Live birth index[d]	98.1 ± 3.3	98.8 ± 2.8 (101)	98.7 ± 2.8 (101)	75.9 ± 26.2[g] (77)
Live pups on Lactation Day 4	14.8 ± 1.8	15.0 ± 1.9 (101)	13.7 ± 1.3 (93)	4.0 ± 5.6[g] (27)
Viability index[e]	99.5 ± 1.8	100.0 ± 0.0 (101)	97.3 ± 3.5 (98)	29.2 ± 40.4[g] (29)

[a]Ministry of Health and Welfare Japan (1999).
[b](Number of live pups born/number of implantation scars) × 100.
[c](Number of pups born/number of implantation scars) × 100 (%).
[d](Number of live pups born/number of pups born) × 100.
[e](Number of live pups on day 4/number of live pups born) × 100.
[f]Significantly different from control ($p < 0.05$); test was not reported.
[g]Significantly different from control ($p < 0.01$); test was not reported.

1

Table B.19. Body Weights of Pups Born to Female Rats Exposed to Sulfolane for 41–50 Days[a]

Parameter		Exposure Group (mg/kg-day)			
		0	60	200	700
Number of dams (except where indicated otherwise)		11	12	10	10
Mean pup weight[b]	Lactational Day 0	6.41 ± 0.33	6.03 ± 0.35 (94)	6.05 ± 0.35 (94)	5.16 ± 0.51[d] (80)
	Lactational Day 4	9.57 ± 0.81	9.41 ± 0.99 (98)	9.43 ± 1.13 (99)	5.96 ± 1.52[d] ($n = 5$) (62)
Litter weight	Lactational Day 0	95.27 ± 11.58	89.83 ± 7.64 (94)	85.11 ± 5.60[c] (89)	59.22 ± 27.00[d] (62)
	Lactational Day 4	141.07 ± 16.51	139.77 ± 10.53 (99)	128.00 ± 8.19[c] (91)	48.94 ± 46.11[d] ($n = 5$) (35)

[a]Ministry of Health and Welfare Japan (1999).
[b]Weights expressed as mean ± SD (% of control).
[c]Significantly different from control ($p < 0.05$); test was not reported.
[d]Significantly different from control ($p < 0.01$); test was not reported.

2

Table B.20. Hematological Parameters of Male and Female Hartley-Derived Guinea Pigs After Inhalation Exposure to Sulfolane for 27 Days[a]

Parameter[c]		Exposure Group, mg/m^3 (Adjusted Daily Concentration, mg/m^3)[b]	
		0[d]	495 (120)
Number of animals[c]		DNP	15
White blood cell count (10^3/mL)	Preexposure	ND	5.9 ± 0.5
	Postexposure (~30 d)	5.8 ± 0.8	4.9 ± 0.3
Hematocrit count (% by volume)	Preexposure	ND	46 ± 0.4
	Postexposure (~30 d)	39 ± 4.8	48 ± 0.5
Hemoglobin count (g/100 mL)	Preexposure	ND	13.9 ± 0.1
	Postexposure (~30 d)	12.4 ± 1.5	15.2 ± 0.1

[a]Andersen et al. (1977c).
[b]Concentration is adjusted for continuous exposure 24 hours/day, 7 days/week.
[c]Values expressed as mean ± SE (% of control); % is calculated; male and female data were not reported separately.
[d]Though data for a "control" group is reported in Table 3 of the study, a control group is not mentioned in the methods explanation; it is unclear what this "control" group represents.
[e]Sample sizes reflect those at the origin of study; hematological data were taken from 9–15 subjects.

DNP = Data not provided by study authors.
ND = Not determined.

1

Table B.21. Hematological Parameters of Male and Female Hartley-Derived Guinea Pigs After Inhalation Exposure to Sulfolane for 85–110 Days[a]

Parameter[c]		Exposure Group, mg/m^3 (Adjusted Daily Concentration, mg/m^3)[b]					
		0[d]	2.8 (2.7)	4.0 (3.8)	20 (19.2)	159 (152)	200 (192)
Exposure duration (d)		DNP	90	110	95	85	90
Number of animals[e]		DNP	DNP	DNP	DNP	15	15
White blood cell count (10^3/mL)	Preexposure	ND	DNP	DNP	DNP	6.8 ± 0.3 (NA)	5.9 ± 0.6 (NA)
	Exposure Day 20	ND	DNP	DNP	DNP	ND	3.1 ± 0.4 (NA)[g]
	Exposure Day 30	5.8 ± 0.8	DNP	DNP	DNP	6.9 ± 0.2 (119)	3.8 ± 0.4 (66)[g]
	Exposure Day 60	4.6 ± 0.8	DNP	DNP	DNP	6.7 ± 0.3 (146)	5.2 ± 0.3 (113)
	Exposure Day 90[f]	6.2 ± 1.1	DNP	DNP	DNP	6.8 ± 0.3 (110)	4.4 ± 0.2[g] (71)
Hematocrit count (% by volume)	Preexposure	ND	DNP	DNP	DNP	46 ± 0.3 (NA)	44 ± 0.4 (NA)
	Exposure Day 20	ND	DNP	DNP	DNP	ND	49 ± 0.9 (NA)
	Exposure Day 30	39 ± 4.8	DNP	DNP	DNP	46 ± 0.3 (118)	51 ± 0.4 (131)
	Exposure Day 60	46 ± 0.5	DNP	DNP	DNP	47 ± 0.3 (102)	47 ± 0.6 (102)
	Exposure Day 90	46 ± 0.8	DNP	DNP	DNP	46 ± 6.3 (100)	47 ± 1.1 (102)
Hemoglobin count (g/100 mL)	Preexposure	ND	DNP	DNP	DNP	16.0 ± 0.1 (NA)	14.4 ± 0.1 (NA)
	Exposure Day 20	ND	DNP	DNP	DNP	ND	14.9 ± 0.2 (NA)
	Exposure Day 30	12.4 ± 1.5	DNP	DNP	DNP	16.8 ± 0.1 (135)	15.5 ± 0.2 (125)
	Exposure Day 60	14.6 ± 0.2	DNP	DNP	DNP	16.9 ± 0.1 (116)	15.1 ± 0.1 (103)
	Exposure Day 90	14.8 ± 0.2	DNP	DNP	DNP	16.6 ± 0.1 (112)	14.6 ± 0.2 (99)

[a]Andersen et al. (1977d).
[b]Concentration is adjusted for continuous exposure 24 hours/day, 7 days/week.
[c]Values expressed as mean ± SE (% of control); % is calculated; male and female data were not reported separately.
[d]Though data for a "control" group is reported in Table 3 of the study, a control group is not mentioned in the methods explanation; it is unclear what this "control" group represents.
[e]Sample sizes reflect those at the origin of study; hematological data were taken from 9–15 subjects at each dose level.
[f]Except for the 159 mg/m^3 exposure-level, which only lasted for a duration of 85 days; observations were made at 85 days for this group.
[g]Significantly different from control ($p < 0.05$); Student's *t*-test.

DNP = Data not provided by study authors.
ND = No data.
NA = Not applicable.

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APPENDIX C. BMD OUTPUTS

No BMD analysis was used to derive reference values.

APPENDIX D. REFERENCES

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